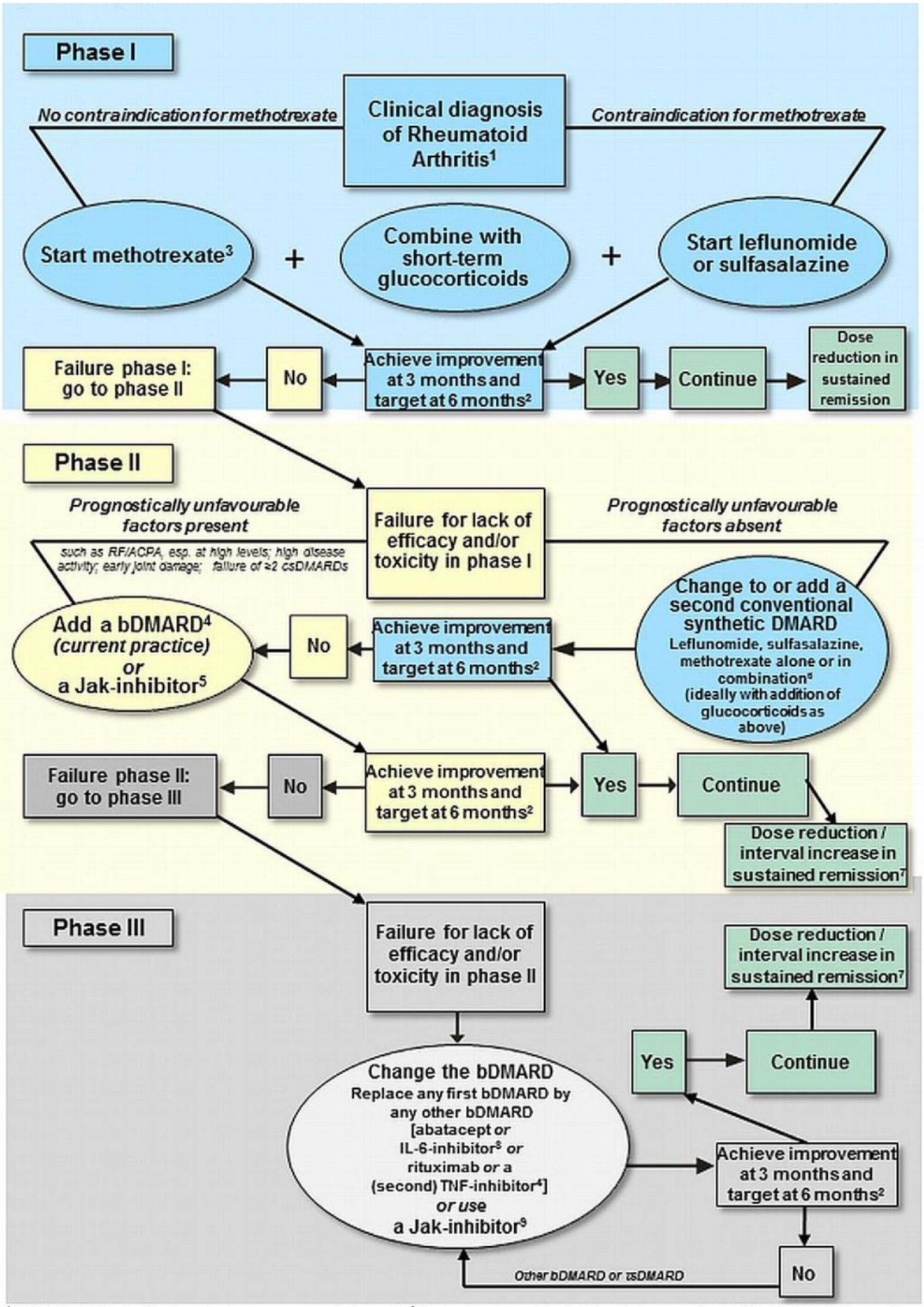
New Updated EULAR/ACR Guidelines & Recommendations 2018-2019

قال رسول الله ﷺ

إذا مات ابن آدم انقطع عملة إلا من ثلاث: صدقة جارية، او علم ينتفع به، او ولد صالح يدعو له.

اسألكم الدعاء

هاله الحضري


Phase I
No contraindication for methotrexate
Clinical diagnosis of Rheumatoid Arthritis[1]
Contraindication for methotrexate
Start methotrexate[3]
+
Combine with short-term glucocorticoids
+
Start leflunomide or sulfasalazine
Failure phase I: go to phase II
No
Achieve improvement at 3 months and target at 6 months[2]
Yes
Continue
Dose reduction in sustained remission
Phase II
Prognostically unfavourable factors present
such as RF/ACPA, esp. at high levels; high disease activity; early joint damage; failure of ≥2 csDMARDs
Failure for lack of efficacy and/or toxicity in phase I
Prognostically unfavourable factors absent
Add a bDMARD[4] (current practice) or a Jak-inhibitor[5]
No
Achieve improvement at 3 months and target at 6 months[2]
Change to or add a second conventional synthetic DMARD
Leflunomide, sulfasalazine, methotrexate alone or in combination[6] (ideally with addition of glucocorticoids as above)
Failure phase II: go to phase III
No
Achieve improvement at 3 months and target at 6 months[2]
Yes
Continue
Dose reduction / interval increase in sustained remission[7]
Phase III
Failure for lack of efficacy and/or toxicity in phase II
Dose reduction / interval increase in sustained remission[7]
Yes
Continue
Change the bDMARD
Replace any first bDMARD by any other bDMARD [abatacept or IL-6-inhibitor[8] or rituximab or a (second) TNF-inhibitor[4]] or use a Jak-inhibitor[9]
Achieve improvement at 3 months and target at 6 months[2]
Other bDMARD or tsDMARD
No

[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3]"Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is

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SPECIAL ARTICLE

2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the health care provider in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes, but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision, as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To develop treatment recommendations for children with juvenile idiopathic arthritis manifesting as non-systemic polyarthritis, sacroiliitis, or enthesitis.

Methods. The Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions were developed and refined by members of the guideline development teams. A systematic review was conducted to compile evidence for the benefits and harms associated with treatments for these conditions. GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to rate the quality of evidence. A group consensus process was conducted among the Voting Panel to generate the final recommendations and grade their strength. A Parent and Patient Panel used a similar consensus approach to provide patient/caregiver preferences for key questions.

Results. Thirty-nine recommendations were developed (8 strong and 31 conditional). The quality of supporting evidence was very low or low for 90% of the recommendations. Recommendations are provided for the use of nonsteroidal antiinflammatory drugs, disease-modifying antirheumatic drugs, biologics, and intraarticular and oral glucocorticoids. Recommendations for the use of physical and occupational therapy are also provided. Specific

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recommendations for polyarthritis address general medication use, initial and subsequent treatment, and adjunctive therapies. Good disease control, with therapeutic escalation to achieve low disease activity, was recommended. The sacroiliitis and enthesitis recommendations primarily address initial therapy and adjunctive therapies.

Conclusion. This guideline provides direction for clinicians, caregivers, and patients making treatment decisions. Clinicians, caregivers, and patients should use a shared decision-making process that accounts for patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.

INTRODUCTION

Juvenile arthritis is one of the most common chronic diseases of childhood, with an estimated prevalence of 1 per 1,000 children (1–3). The term juvenile idiopathic arthritis (JIA) defines a heterogeneous collection of inflammatory arthritides of unknown etiology with onset prior to age 16 years and a minimum duration of 6 weeks, following the exclusion of other known causes of synovitis (4). Current International League of Associations for Rheumatology (ILAR) classification criteria divide JIA into 7 mutually exclusive categories defined by the number of joints involved, presence or absence of extraarticular manifestations, and presence or absence of additional markers including rheumatoid factor (RF) and HLA–B27 (4).

All forms of JIA are associated with decreased health-related quality of life and risk of permanent joint damage, and the disease may persist into adulthood, causing ongoing significant morbidity and impaired quality of life (5–13). A number of treatments are available, including nonsteroidal antiinflammatory drugs (NSAIDs), systemic and intraarticular glucocorticoids, and nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs). Prompt initiation of appropriate therapy is of critical importance in preventing permanent damage and improving outcomes. While earlier disease recognition and expanded treatment options have made good disease control a possibility for many patients, they have also made the decision-making regarding treatments more complex for physicians, caregivers, and patients.

The American College of Rheumatology (ACR) published initial recommendations for JIA in 2011 that provided guidance for the treatment of JIA and for the monitoring of select medical therapies, and an update in 2013 focused on the treatment of systemic arthritis (14,15). The ACR has subsequently transitioned from the RAND/UCLA Appropriateness Method used to generate these prior recommendations to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, which has the advantages of a more transparent decision-making process and well-defined criteria for moving from evidence to recommendation, including balancing benefits and harms and consideration of patient values and preferences while maintaining methodologic rigor (16).

The goal of this guideline project was to provide updated recommendations for juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis, incorporating recently published data and utilizing the GRADE methodology. Recommendations for the treatment of chronic and acute JIA-associated uveitis were developed concomitantly and are presented separately (17).

METHODS

Methodology overview. This guideline followed the ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes using the GRADE methodology (www.gradeworkinggroup.org) to rate the quality of the available evidence and to develop the recommendations (18–20). ACR policy guided disclosures and the management of conflicts of interest (participant disclosures are available at https://www.rheumatology.org/Portals/0/Files/JIA-Guideline-Disclosures.pdf). Supplementary Appendix 1, available on the *Arthritis & Rheumatology* web site

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Dr. Beukelman has received consulting fees from Bristol-Myers Squibb, Sobi, UCB, and Novartis (less than $10,000 each). Dr. Lovell has received consulting fees from AstraZeneca, Amgen, Abbott, Wyeth Pharmaceuticals, Pfizer, Hoffmann-La Roche, Novartis, UCB, Takeda, Janssen, GlaxoSmithKline, Boehringer Ingelheim, Celgene, Bristol-Myers Squibb, and AbbVie (less than $10,000 each). Dr. Nigrovic has received consulting fees from Bristol-Myers Squibb, Pfizer, AbbVie, Novartis, and Sobi (less than $10,000 each) and research grants from Sobi, Novartis, AbbVie, and Genentech (in support of the FROST study of systemic JIA through CARRA). Dr. Stoll has received speaking fees from Novartis (less than $10,000). Dr. Rabinovich has received consulting fees from AbbVie (less than $10,000). Dr. Schneider has received consulting fees from Novartis and Sobi (less than $10,000 each). No other disclosures relevant to this article were reported.

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at http://onlinelibrary.wiley.com/doi/10.1002/art.40884/abstract, describes the methods in detail.

Guideline development teams. This work involved 5 teams: 1) a Core Leadership Team, consisting of 4 pediatric rheumatologists, who supervised and coordinated the project and assisted with developing the scope of the project and initial Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions and drafting the manuscript; 2) a Literature Review Team, led by an experienced literature review consultant, which completed the literature search and data abstraction and rated the quality of evidence; 3) an Expert Panel, composed of 9 pediatric rheumatologists, who assisted with developing the scope of the project and drafting and refining the PICO questions; 4) a Voting Panel, consisting of 15 pediatric rheumatologists and 2 adult patients with JIA, who assisted with developing the scope of the project and refining the PICO questions and voted on the recommendations; and 5) a Parent and Patient Panel, consisting of 9 adult patients with JIA and 2 parents of children with JIA, who reviewed the collated evidence and provided input on their values and preferences within the context of a separate meeting. Supplementary Appendix 2 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40884/abstract) presents rosters of the team and panel members. In accordance with ACR policy, the principal investigators and the literature review consultant were free of potential conflicts of interest, and in all teams, >50% of members were free of potential conflicts of interest.

PICO question development and importance of outcomes. The Core Leadership Team drafted the initial project scope, key principles, and examples of relevant PICO questions. The following topics were proposed to the guideline development groups for consideration: acute and chronic anterior uveitis, oligoarthritis, polyarthritis, systemic arthritis, sacroiliitis, enthesitis, and temporomandibular joint arthritis. PICO questions for each topic were developed and discussed at a face-to-face meeting during which the topics were refined. The project scope was subsequently limited to patients with non-systemic polyarthritis, sacroiliitis, and enthesitis, because these were deemed to be the most high-impact areas. The PICO questions for these topics were subsequently reviewed and further refined by the Expert and Voting Panels via e-mail.

Populations (Table 1). While the current ILAR classification criteria have been useful for identifying homogeneous groups of patients for research, more recent data suggest that these categories may not entirely reflect the underlying genetic and clinical heterogeneity of the disease or be relevant for guiding treatment decisions (20–22). For this reason, it was decided to base the current guideline on broad clinical phenotypes rather than ILAR categories, similar to the approach used for development of the 2011 guideline (15). The patient populations addressed in this guideline are defined below. The current recommendations are intended to address typical

Table 1. Terms and definitions*

Term	Definition
Polyarthritis population	Children with JIA and non-systemic polyarthritis (≥5 joints ever involved); may include children from ILAR JIA categories of polyarticular (rheumatoid factor positive or negative), extended oligoarticular, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis.
Risk factors	One or more of the following: positive rheumatoid factor, positive anti–cyclic citrullinated peptide antibodies, joint damage.
Moderate/high disease activity	Clinical Juvenile Disease Activity Score based on the cJADAS-10 >2.5.
Low disease activity	Clinical JADAS-10 ≤2.5 and ≥1 active joint.
Sacroiliitis population	Patients with active sacroiliitis who will most likely be classified within the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis, but may include patients in any of the ILAR JIA categories.
Active sacroiliitis	Prior or current magnetic resonance imaging findings consistent with sacroiliitis along with clinical examination findings consistent with sacroiliitis (e.g., pain with direct palpation of the sacroiliac joints) and/or patient-reported symptoms of inflammatory back pain.
Enthesitis population	Patients with enthesitis (inflammation at tendon-to-bone insertion sites) who will most likely be from the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis, but may include patients from any of the ILAR JIA categories.
Active enthesitis	Tenderness and/or swelling of the entheses determined to require medical treatment per the treatment provider.

* Disease activity (moderate/high and low) as defined by the clinical Juvenile Disease Activity Score based on 10 joints (cJADAS-10) is provided as a general parameter and should be interpreted within the clinical context. JIA = juvenile idiopathic arthritis. ILAR = International League of Associations for Rheumatology.

patients with the phenotype and may not be applicable to patients with uncommon features or highly refractory disease.

Polyarthritis. This group includes children with JIA and polyarthritis (≥5 joints ever involved) and may include children from different ILAR JIA categories but excludes children with systemic arthritis or sacroiliitis. These guidelines are not intended to be applicable to children with associated extraarticular manifestations (e.g., psoriasis, uveitis, inflammatory bowel disease) that may also influence treatment decisions. Given the heterogeneity of patients with JIA and polyarthritis, the Expert and Voting Panels initially categorized patients into treatment groups, using combinations of the following categories: 1) presence or absence of risk factors for disease severity and potentially a more refractory disease course, and 2) low disease activity versus moderate/high disease activity.

Risk factors were defined as the presence of one or more of the following: positive anti–cyclic citrullinated peptide antibodies, or joint damage. The Juvenile Arthritis Disease Activity Score (JADAS) was proposed as a means of categorizing disease activity, with the acknowledgment that a number of versions exist, and that validation is not fully complete and cutoff scores may change (23–27). A joint with inactive disease was defined using the ACR definition: presence of swelling (not due to currently inactive synovitis or to bony enlargement) or, if swelling is not present, limitation of motion accompanied by pain, tenderness, or both (28,29). The Voting Panel used the clinical JADAS based on 10 joints (cJADAS-10) and a cutoff of ≤2.5 versus >2.5 to define low versus high/moderate disease activity. Low disease activity was further defined as a cJADAS-10 of ≤2.5 and ≥1 joint with active disease to ensure that active arthritis was also present. Moderate and high disease activity were considered together, because it was thought that treatment approaches would be similar (30). The cJADAS-10 is a sum of the total active joint count (to a maximum of 10), physician's global assessment of disease activity (0–10 scale), and parent/patient's global assessment of well-being (0–10 scale). It was also acknowledged that one of the limitations of the JADAS is the lack of standardization of the physician's and parent's global assessments. It is therefore recommended that the JADAS be interpreted within the context of the clinical presentation rather than considered an absolute determinant of disease activity.

Because ultimately few data were available to support different treatment approaches based on the risk factors and disease activity categories, patients were often grouped together to provide a recommendation. The few instances in which the Voting Panel made differing recommendations based on disease activity or risk factors are explicitly noted.

Sacroiliitis. This group includes patients with active sacroiliitis who will most likely be classified within the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis but may include patients in any of the ILAR JIA categories. In addition to active sacroiliitis, patients may or may not have active peripheral joint disease and/or enthesitis to be included in this population. It is anticipated that patients with peripheral spondyloarthritis and no sacroiliitis would be treated according to the polyarthritis recommendations included in this update or existing JIA oligoarthritis treatment recommendations from the 2011 ACR JIA guideline (15), depending on the numbers of joints involved. For the purposes of this guideline, patients were considered to have active sacroiliitis if they had prior or current magnetic resonance imaging findings consistent with sacroiliitis along with clinical examination findings consistent with sacroiliitis (e.g., pain with direct palpation of the sacroiliac joints) and/or patient-reported symptoms of inflammatory back pain.

Enthesitis. This group is intended to include patients with enthesitis (inflammation at tendon-to-bone insertion sites) who will also most likely be from the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis but may include patients from any of the ILAR JIA categories. Patients may or may not have concomitant active peripheral arthritis or sacroiliitis to be included in this guideline, but the recommendations for enthesitis are intended to apply to patients with isolated enthesitis or with active enthesitis despite adequate control of their other disease manifestations. For the purposes of this guideline, active enthesitis is tenderness and/or swelling of the entheses determined to require medical treatment per the treating provider.

Interventions. The pharmacologic and nonpharmacologic therapies considered are listed in Table 2. Both intraarticular and oral glucocorticoids were considered. For the purposes of the recommendations, a bridging course of oral glucocorticoids was defined as a short course (<3 months) of oral glucocorticoids intended to control disease activity quickly during escalation of DMARD or biologic therapy, using the shortest possible duration and the lowest dose needed to control symptoms. The duration of bridging therapy would likely be primarily determined by the anticipated timing of onset of action of the other DMARD or biologic treatment(s). An optimal trial of methotrexate was considered to be 3 months; however, if no or minimal response was observed after 6–8 weeks, it was agreed that changing or adding therapy may be appropriate.

Outcomes. Outcomes were selected during the initial face-to-face scoping meeting and subsequently refined by online vote (Supplementary Appendix 3**,** available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40884/abstract). Critical outcomes included disease activity, quality of life, joint damage, and serious adverse events. Pain was selected as an important outcome. While each of these outcomes was thought to be important in decision-making by the guideline development teams, they were not routinely reported across stud-

Table 2. Interventions included in the literature review*

Intervention	Name/type
NSAIDs	Any
DMARDs	Leflunomide, methotrexate, sulfasalazine, triple non–biologic DMARD (methotrexate, sulfasalazine, hydroxychloroquine)
Biologics	
TNFi	Adalimumab, etanercept, infliximab, golimumab†
Non-TNFi‡	Abatacept (CTLA-4Ig), tocilizumab (anti–interleukin-6 receptor), rituximab (anti-CD20)
Glucocorticoids	
Oral	Any
Intraarticular	Triamcinolone acetonide, triamcinolone hexacetonide, methylprednisolone acetate
Other interventions	Physical therapy
	Occupational therapy

* NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs; TNFi = tumor necrosis factor inhibitor.
† Certolizumab was not included in the recommendations because no pediatric data were yet available.
‡ Evaluated for polyarthritis only.

ies. Disease activity and serious adverse events were the most consistently reported outcomes.

Literature searches, data abstraction, and rating the quality of evidence. Systematic searches of the published English-language literature included Ovid Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the beginning of each database through June 12, 2017 (see Supplementary Appendix 4**,** available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40884/abstract); updated searches were conducted on October 13, 2017. DistillerSR software (https://distillercer.com/products/distillersr-systematic-reviewsoftware/) facilitated duplicate screening of literature search results. Supplementary Appendix 5, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40884/abstract, shows the citation flow chart. Reviewers entered extracted data into RevMan software (http://tech.cochrane.org/revman) and evaluated the risk of bias of primary studies using the Cochrane risk of bias tool (http://handbook.cochrane.org/). RevMan files were exported into GRADEpro software to formulate a table showing the GRADE summary of findings (Supplementary Appendix 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40884/abstract) for each PICO question (31).

When available, the evidence summaries included the benefits and harms for outcomes of interest across studies, the relative effect (95% confidence interval), the number of participants, and the absolute effects. GRADE criteria provided the framework for judging the overall quality of evidence (16). The Literature Review Team rated the quality of evidence for each critical and important outcome as high, moderate, low, or very low quality, taking into account limitations of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The overall quality listed in this report for a body of evidence (i.e., either an individual article or a group of articles) is not a statement about the methodologic quality of the study (or studies). Rather, the intention was to rate the article(s) in relation to the PICO question under consideration. As a result, a very well-conducted study might be rated lower in the evidence report. For example, if the population or intervention being studied does not completely match the population or intervention being examined by the PICO question, the evidence is downgraded for indirectness. The overall quality of evidence may also be downgraded due to imprecision in the effect estimate (e.g., wide confidence intervals or a low number of patients or events).

During the Voting Panel meeting, the panel also considered relevant data from adult studies, but these studies were not systematically searched or compiled in the evidence report. The Voting Panel was provided with a copy of the evidence report from the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis as a reference (32) (https://www.rheumatology.org/Portals/0/Files/Axial-SpA-Guideline-Supplement-E.pdf).

Moving from evidence to recommendations. Each recommendation was made based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (e.g., confidence in the effect estimates), and patients' values and preferences, as per GRADE methodology. Discussion points and voting results from the Parent and Patient Panel meeting were presented during the Voting Panel meeting, as relevant. When the literature did not clearly guide recommendations, recommendations were based on the experience of the Voting Panel members (including physicians and the 2 patients present) as well as the results from the Parent and Patient Panel. Financial costs were not formally considered during the voting process.

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. Recommendations required a 70% level of

agreement; if 70% agreement was not achieved during an initial vote, the panel members held additional discussions before re-voting, including rewording of recommendations if needed, until consensus was attained (33). Discussion and iterative voting occurred until consensus was achieved. An additional round of voting was conducted online after the Voting Panel meeting to address questions that arose during preparation of the final recommendations. For each recommendation, a written explanation is provided, describing the reasons for this decision and conditions under which the alternative choice may be preferable, when relevant.

Moving from recommendations to practice. These recommendations are designed to help health care providers, caregivers, and patients engage in shared decision-making regarding treatment choices. Health care providers, caregivers, and patients must take into consideration not only clinical phenotype and level of disease activity but also comorbidities, response to and tolerance of prior therapies, patient's values and preferences, and patient's functional status and functional goals when choosing the optimal therapy for an individual patient at the given point in treatment.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations (18–20)

1. A *strong* recommendation means that the Voting Panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation. In some cases, strong recommendations were made even in the absence of moderate- or high-quality evidence based on Voting Panel experience and data from adult studies.
2. A *conditional* recommendation means that the Voting Panel believed that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are particularly preference-sensitive and warrant a shared decision-making approach. Conditional recommendations were generally based on low- to very low–quality evidence. Most recommendations in this guideline are conditional.
3. For each recommendation, Supplementary Appendix 6 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40884/abstract) provides details regarding the PICO questions and the GRADE evidence tables. PICO questions were combined when possible to create simplified recommendations.

General recommendations for patients with JIA and polyarthritis (Table 3)

For this population, an initial set of general recommendations was made regarding NSAID, DMARD, intraarticular glucocorticoid, and biologic use. These general recommendations are intended to apply to the subsequent specific polyarthritis recommendations addressing these medications, because the recommendations were not anticipated to differ based on initial versus subsequent therapy, level of disease activity, or presence or absence of risk factors. For example, in PICO A.2 and A.3, methotrexate is conditionally recommended over leflunomide and sulfasalazine. It is intended that this recommendation apply to subsequent recommendations referring to DMARD therapy.

Each recommendation in this section is prefaced with the statement "In children and adolescents with JIA and active polyarthritis…"

PICO A.1. *NSAIDs are conditionally recommended as adjunct therapy*. This recommendation is conditional based on the very low quality of evidence and incorporation of patient and caregiver preferences, particularly concerns regarding medication adverse effects. In general, NSAIDs were thought to be appropriate for symptom management, particularly during initiation or escalation of therapy with DMARDs or biologics (34–36). It was acknowledged that NSAIDs are not appropriate as monotherapy for chronic, persistent synovitis.

PICO A.2–A.3. *Using methotrexate is conditionally recommended over leflunomide or sulfasalazine*.

Leflunomide. The quality of supporting evidence for this recommendation was moderate. The recommendation to favor methotrexate over leflunomide is due to the greater volume of data supporting the effectiveness of methotrexate. The Voting Panel also specifically noted the lack of data for the dosing, safety, and effectiveness of leflunomide in children younger than age 3 years and lack of long-term safety data for leflunomide in general for children with polyarthritis (37,38). In addition, there currently is no liquid form of this medication, which may make administration difficult, particularly in younger children.

Sulfasalazine. The recommendation for methotrexate over sulfasalazine is conditional, because the supporting evidence is of very low quality, there are no head-to-head comparison studies, and there are more data supporting the effectiveness of methotrexate. There were also concerns raised by the Voting Panel regarding the safety of sulfasalazine as compared to methotrexate, specifically the risk of Stevens-Johnson syndrome and bone marrow suppression (35,36).

Although methotrexate is conditionally recommended over each of these therapies, it is important to note that the Parent and Patient Voting Panel participants stated that they would want to be made aware of available alternatives to methotrexate, because

Table 3. General medication recommendations for children and adolescents with JIA and polyarthritis*

Recommendation	Level of evidence
Each recommendation is preceded by the phrase: *"In children and adolescents with JIA and active polyarthritis…"*	
NSAIDs	
• NSAIDs are conditionally recommended as adjunct therapy (PICO A.1).	Very low
DMARDs	
• Using methotrexate is conditionally recommended over leflunomide or sulfasalazine (PICO A.2, A.3).	Moderate (leflunomide); very low (sulfasalazine)
• Using subcutaneous methotrexate is conditionally recommended over oral methotrexate (PICO A.4).	Very low
Glucocorticoids	
• Intraarticular glucocorticoids are conditionally recommended as adjunct therapy (PICO A.5).	Very low
• Triamcinolone hexacetonide is ***strongly*** recommended over triamcinolone acetonide for intraarticular glucocorticoid injections (PICO A.6).	Moderate
• Bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy in patients *with high or moderate disease activity* is conditionally recommended (PICO A.7).† Bridging therapy may be of most utility in the setting of limited mobility and/or significant symptoms.	Very low
• Conditionally recommend *against* bridging therapy with a limited course of oral glucocorticoids (<3 months) in patients with *low disease activity* (PICO A.8).	Very low
• ***Strongly*** recommend *against* adding chronic low-dose glucocorticoid, irrespective of risk factors or disease activity (PICO A.9).	Very low
Biologic DMARDs	
• In children and adolescents with JIA and polyarthritis initiating treatment with a biologic (etanercept, adalimumab, golimumab, abatacept, or tocilizumab) combination therapy with a DMARD is conditionally recommended over biologic monotherapy (PICO A.10, A.11, A.12, A.13, A.14).	Very low (etanercept, golimumab); low (abatacept, tocilizumab); moderate (adalimumab)
• Combination therapy with a DMARD is ***strongly*** recommended for infliximab (PICO A.15).	Low
Physical therapy and occupational therapy	
• In children and adolescents with JIA and polyarthritis who have or are at risk of functional limitations, using physical therapy and/or occupational therapy is conditionally recommended (PICO A.16, PICO A.17).	Low (physical therapy); very low (occupational therapy)

* JIA = juvenile idiopathic arthritis; NSAIDs = nonsteroidal antiinflammatory drugs; PICO = Patient/Population, Intervention, Comparison, and Outcomes; DMARDs = disease-modifying antirheumatic drugs.
† A bridging course of oral glucocorticoids was defined as a short course (<3 months) of oral glucocorticoids intended to control disease activity quickly during the initiation or escalation of therapy. An adequate trial of methotrexate was considered to be 3 months. If no or minimal response is observed after 6–8 weeks, it was agreed that changing or adding therapy may be appropriate.

the adverse effects of methotrexate, particularly gastrointestinal intolerance, are very limiting for some children.

PICO A.4. *Using subcutaneous methotrexate is conditionally recommended over oral methotrexate*. This recommendation is conditional, because the supporting evidence is of very low quality, and patient preferences may guide the choice of route of administration (39–46). The strength of the recommendation also reflects Voting Panel experience, lack of certainty regarding differences in adverse event rates between the 2 routes of administration, consideration of data suggesting variable bioavailability of oral methotrexate (particularly at higher doses), and the goal of optimizing methotrexate effectiveness prior to escalating therapy (47,48).

PICO A.5. *Intraarticular glucocorticoids are conditionally recommended as adjunct therapy*. This recommendation is conditional given that the supporting evidence is of very low quality and was primarily generated in children with oligoarthritis, and given the variable parent and patient experiences and preferences regarding a procedure that may require sedation or be painful (49). In addition, intraarticular glucocorticoid injections may not be an appropriate treatment approach for large numbers of joints or joints that have been injected multiple times; escalation of systemic therapy may be preferred in these situations. The Voting Panel also suggested that intraarticular glucocorticoid injections be more strongly considered when arthritis is preventing ambulation or otherwise interfering with important daily activities and more prompt disease control is needed.

Table 4. General guidelines for the initial and subsequent treatment of children and adolescents with JIA and polyarthritis*

Recommendation†	Level of evidence
Each recommendation is preceded by the phrase: ***"In children and adolescents with JIA and active polyarthritis…"***	
Initial therapy	
All patients	
• Initial therapy with a DMARD is ***strongly*** recommended over NSAID monotherapy (PICO B.1).	Moderate
• Using methotrexate monotherapy as initial therapy is conditionally recommended over triple DMARD therapy (PICO B.2).	Low
Patients without risk factors:†	
• Initial therapy with a DMARD is conditionally recommended over a biologic (PICO B.3).	Low
Patients with risk factors:	
• Initial therapy with a DMARD is conditionally recommended over a biologic, recognizing that there are situations where initial therapy that includes a biologic may be preferred (PICO B.4). Initial biologic therapy may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, or hip), high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage.	Low
Subsequent therapy: Low disease activity (cJADAS-10 ≤2.5 and ≥1 active joint) For children receiving a DMARD and/or biologic:	
• Escalating therapy is conditionally recommended over no escalation of therapy (PICO B.5, B.6). Escalation of therapy may include: Intraarticular glucocorticoid injection(s), optimization of DMARD dose, trial of methotrexate if not done, and adding or changing biologic.	Very low
Subsequent therapy: Moderate/high disease activity (cJADAS-10 >2.5)	
If patient is receiving DMARD monotherapy:	
• Adding a biologic to original DMARD is conditionally recommended over changing to a second DMARD (PICO B.7).	Low
• Adding a biologic is conditionally recommended over changing to triple DMARD therapy (PICO B.8).	Low
If patient is receiving first TNFi (± DMARD):	
• Switching to a non-TNFi biologic (tocilizumab or abatacept) is conditionally recommended over switching to a second TNFi (PICO B.9). A second TNFi may be appropriate for patients with good initial response to their first TNFi (i.e., secondary failure).	Very low
If patient is receiving second biologic:	
• Using TNFi, abatacept, or tocilizumab (depending on prior biologics received) is conditionally recommended over rituximab (PICO B.10).	Very low

* Disease activity (moderate/high and low) as defined by the clinical Juvenile Disease Activity Score based on 10 joints (cJADAS-10) is provided as a general parameter and should be interpreted within the clinical context. TNFi = tumor necrosis factor (etanercept, adalimumab, infliximab, golimumab) (see Table 3 for other definitions).
† Risk factors include the presence of any of the following: positive anti–cyclic citrullinated peptide antibodies, positive rheumatoid factor, or presence of joint damage. An adequate trial of methotrexate was considered to be 3 months. If no or minimal response is observed after 6–8 weeks, it was agreed that changing or adding therapy may be appropriate. For the purposes of these recommendations, triple DMARD therapy is methotrexate, sulfasalazine, and hydroxychloroquine. The term biologic refers to TNFi, abatacept, or tocilizumab for each of the recommendations, with the exception of PICO B.10, which includes rituximab. Shared decision-making between the physician, parents, and patient, including discussion of recommended treatments and potential alternatives, is recommended when initiating or escalating treatment.

PICO A.6. *Triamcinolone hexacetonide is **strongly** recommended over triamcinolone acetonide for intraarticular glucocorticoid injections*. The quality of supporting evidence for this recommendation was moderate (50). This recommendation was further supported by observational studies showing improved outcomes with triamcinolone hexacetonide in oligoarticular JIA and rheumatoid arthritis (RA) (51,52). Voting panel members specifically noted their consistent and repeated observation of more complete and longer duration of clinical response without increased adverse effects with triamcinolone hexacetonide versus triamcinolone acetonide. The Parent and Patient Voting Panel also supported this judgment on the strength of the recommendation.

PICO A.7. *Bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy in patients with high or moderate disease activity is conditionally recommended*. This recommendation is conditional based on very low quality of supporting evidence and the known risks associated with systemic glucocorticoid treatment. Parents and patients agreed that bridging therapy was acceptable in this setting. Bridging therapy with glucocorticoids may have most utility

in the setting of high disease activity, limited mobility, and/or significant symptoms.

PICO A.8. *Conditionally recommend **against** bridging therapy with a limited course of oral glucocorticoids (<3 months) in patients with low disease activity*. The quality of evidence for this recommendation was very low. Intraarticular glucocorticoid injection was considered preferable in this setting.

PICO A.9. ***Strongly** recommend **against** adding chronic low-dose glucocorticoids, irrespective of risk factors or disease activity*. The quality of supporting evidence for this recommendation was very low. The recommendation was strong, however, given the known adverse effects of long-term systemic glucocorticoid treatment in children, particularly growth suppression, weight gain, osteopenia and cataracts, and availability of other treatment options. The Voting Panel agreed that in the setting of low disease activity, targeted joint injections may be more appropriate (PICO A.5). In the setting of moderate or high disease activity, escalating DMARD or biologic therapy is likely more appropriate.

PICO A.10–A.14. *In children and adolescents with JIA and polyarthritis initiating treatment with a biologic (etanercept, adalimumab, golimumab, abatacept, or tocilizumab), combination therapy with a DMARD is conditionally recommended over biologic monotherapy*. This recommendation is intended for patients initiating biologics for additional disease control and not intended for patients who may be tapering therapy due to inactive disease, for whom tapering or removal of the DMARD while continuing biologic therapy may be an appropriate strategy. The available evidence addresses combination therapy with methotrexate, with no evidence identified for other DMARDs. There was variability in the quality of supporting evidence for the medications, ranging from very low (etanercept, golimumab) to low (abatacept or tocilizumab) and moderate (adalimumab) (39,53–67). The potential benefit of methotrexate treatment for prevention of antidrug antibodies to adalimumab was included in the discussion for concomitant DMARD use with that medication (61). The overall recommendation is conditional based on the quality of supporting evidence and variable parent and patient preferences given the burden of taking multiple medications and concerns regarding methotrexate intolerance. The Voting Panel recognized that there may be situations in which biologic monotherapy is also acceptable, particularly in the setting of adequate disease control or methotrexate intolerance.

PICO A.15. *Combination therapy with a DMARD is **strongly** recommended for infliximab*. Using infliximab in combination with a DMARD was a strong recommendation despite the low quality of evidence, primarily given more extensive experience with the need for combination therapy to reduce the risk of antidrug antibody formation (68,69).

PICO A.16, A.17. *In children and adolescents with JIA and polyarthritis who have or are at risk for functional limitations, using physical therapy (PT) and/or occupational therapy (OT) is conditionally recommended*. This recommendation is conditional based on the low quality of supporting evidence for PT, very low level of evidence for OT, and Voting Panel experience (70,71).

Recommendations for the initial and subsequent treatment of JIA and polyarthritis (Table 4 and Figure 1)

While the initial set of PICO questions for polyarthritis also included comparisons between specific biologics, these questions were discarded at the in-person Voting Panel meeting due to lack of evidence to guide decision-making in those scenarios. Although there is most experience with tumor necrosis factor inhibitors (TNFi) as the initial biologic, the class of initial biologic is not specified in the recommendations, again due to lack of comparative data, and the consideration that non-TNFi biologics may be preferred in certain scenarios based on patient-level factors (e.g., family history of demyelinating disease) and preferences. In the recommendations (see below), biologic therapy refers to TNFi, abatacept, or tocilizumab, with the exception of PICO B.9, in which rituximab is also addressed. Each recommendation in this section is prefaced with the statement "In children and adolescents with JIA and active polyarthritis…"

Initial therapy

PICO B.1 *Initial therapy with a DMARD is **strongly** recommended over NSAID monotherapy*. This recommendation is strong based on moderate quality of supporting evidence, known risk of permanent joint damage associated with ongoing, active disease, and Voting Panel experience (35,36,41).

PICO B.2. *Using methotrexate monotherapy as initial therapy is conditionally recommended over triple DMARD therapy*. The quality of evidence for this recommendation was low, based on the available trial being relatively small and not blinded (72). Parents and patients also expressed concerns about the burden of taking the 3 different medications, but they did state a preference to be informed about this treatment option.

PICO B.3. *For patients <u>without</u> risk factors, initial therapy with a DMARD is conditionally recommended over a biologic*. This recommendation is conditional based on low quality of supporting evidence and parent and patient differing preferences regarding the risks and benefits of DMARDs and biologics. While initial treatment with a biologic has been studied in TREAT-JIA (Trial of Early Aggressive Therapy in Polyarticular JIA) and ACUTE-JIA (Aggressive Combination Drug Therapy in Early Polyarticular JIA), the results were not thought to be conclusive enough to support

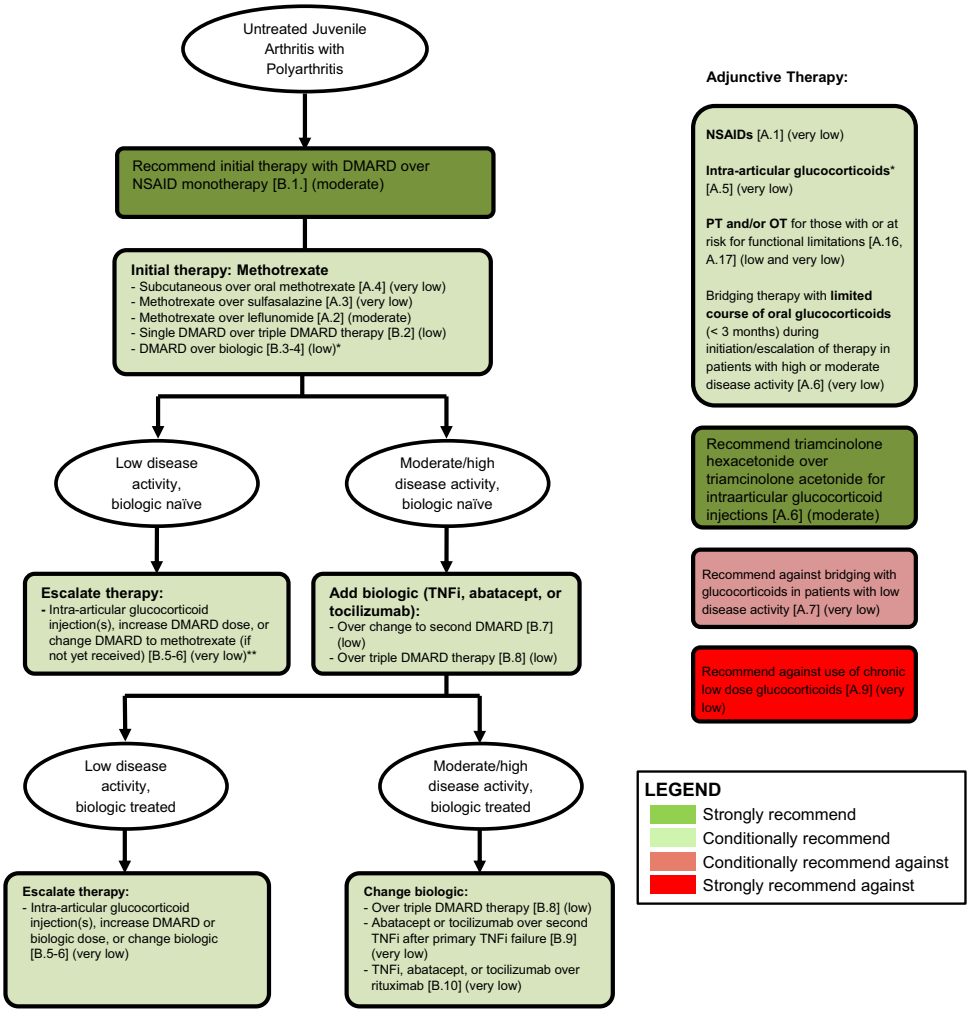
Untreated Juvenile Arthritis with Polyarthritis
Recommend initial therapy with DMARD over NSAID monotherapy [B.1.] (moderate)
Initial therapy: Methotrexate
- Subcutaneous over oral methotrexate [A.4] (very low)
- Methotrexate over sulfasalazine [A.3] (very low)
- Methotrexate over leflunomide [A.2] (moderate)
- Single DMARD over triple DMARD therapy [B.2] (low)
- DMARD over biologic [B.3-4] (low)*
Low disease activity, biologic naïve
Moderate/high disease activity, biologic naïve
Escalate therapy:
- Intra-articular glucocorticoid injection(s), increase DMARD dose, or change DMARD to methotrexate (if not yet received) [B.5-6] (very low)**
Add biologic (TNFi, abatacept, or tocilizumab):
- Over change to second DMARD [B.7] (low)
- Over triple DMARD therapy [B.8] (low)
Low disease activity, biologic treated
Moderate/high disease activity, biologic treated
Escalate therapy:
- Intra-articular glucocorticoid injection(s), increase DMARD or biologic dose, or change biologic [B.5-6] (very low)
Change biologic:
- Over triple DMARD therapy [B.8] (low)
- Abatacept or tocilizumab over second TNFi after primary TNFi failure [B.9] (very low)
- TNFi, abatacept, or tocilizumab over rituximab [B.10] (very low)
Adjunctive Therapy:
NSAIDs [A.1] (very low)
Intra-articular glucocorticoids* [A.5] (very low)
PT and/or OT for those with or at risk for functional limitations [A.16, A.17] (low and very low)
Bridging therapy with limited course of oral glucocorticoids (< 3 months) during initiation/escalation of therapy in patients with high or moderate disease activity [A.6] (very low)
Recommend triamcinolone hexacetonide over triamcinolone acetonide for intraarticular glucocorticoid injections [A.6] (moderate)
Recommend against bridging with glucocorticoids in patients with low disease activity [A.7] (very low)
Recommend against use of chronic low dose glucocorticoids [A.9] (very low)
LEGEND
Strongly recommend
Conditionally recommend
Conditionally recommend against
Strongly recommend against

Figure 1. Summary of primary recommendations for the initial and subsequent treatment of children with juvenile idiopathic arthritis (JIA) and active polyarthritis (see also Tables 3 and 4; for patients with sacroiliitis and/or enthesitis, see also Tables 5 and 6). The clinical Juvenile Arthritis Disease Activity Score based on 10 joints (cJADAS-10) was used to define low disease activity (≤2.5 with ≥1 active joint) versus moderate/high disease activity (>2.5). Although it is provided as a general parameter, the cJADAS-10 should be interpreted within the clinical context. An adequate trial of methotrexate was considered to be 3 months. If no or minimal response is observed after 6–8 weeks, it was agreed that changing or adding therapy may be appropriate. Shared decision-making between the physician, parents, and patient, including discussion of recommended treatments and potential alternatives, is recommended when initiating or escalating treatment. The Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions are shown in brackets, and quality of evidence is shown in parentheses. DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal antiinflammatory drug; PT = physical therapy; OT = occupational therapy; TNFi = tumor necrosis factor inhibitor. *DMARD therapy (methotrexate, leflunomide, or sulfasalazine) over biologic recommendation for patients without and those with risk factors, although initial biologic therapy may be appropriate for some patients with risk factors and involvement of high-risk joints, high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage. **Adding a biologic may be considered in biologic-naive patients with continued low disease activity after escalating therapy (not formally addressed in the guidelines).

biologics as initial therapy for low-risk patients (40,72). Of note, the majority of the Parent and Patient Panel voted against DMARDs as initial therapy, because a number of the participants had considerable adverse effects with methotrexate and had experienced better outcomes with biologics.

PICO B.4. *For patients with risk factors, initial therapy with a DMARD is conditionally recommended over a biologic, recognizing that there are situations where initial therapy that includes a biologic may be preferred*. This recommendation is conditional based on the low quality of supporting evidence and parent and patient differing preferences regarding the risks and benefits of DMARDs and biologics. While initial treatment with a biologic has been studied in TREAT-JIA and ACUTE-JIA, the results were not thought to be conclusive enough to support biologics as initial therapy (40,72). However, the Voting Panel acknowledged that biologics may be appropriate initial therapy for some patients *with risk factors* and involvement of high-risk joints (e.g.,

Table 5. Recommendations for the initial and subsequent treatment of children and adolescents with JIA and sacroiliitis*

Recommendation	Level of evidence
In children and adolescents with active sacroiliitis, treatment with an NSAID is ***strongly*** recommended over no treatment with an NSAID (PICO C.1).	Very low
In children and adolescents with active sacroiliitis despite treatment with NSAIDs:	
• Adding TNFi is ***strongly*** recommended over continued NSAID monotherapy (PICO C.2).	Low
• Using sulfasalazine for patients who have contraindications to TNFi or have failed more than one TNFi is conditionally recommended (PICO C.3).	Low
• ***Strongly*** recommend *against* using methotrexate monotherapy (PICO C.4).	Very low
Glucocorticoids	
In children and adolescents with active sacroiliitis despite treatment with NSAIDs:	
• Bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy is conditionally recommended (PICO C.5).† Bridging therapy may be of most utility in the setting of high disease activity, limited mobility, and/or significant symptoms.	Very low
• Intraarticular glucocorticoid injection of the sacroiliac joints as adjunct therapy is conditionally recommended (PICO C.6).	Very low
Physical therapy	
• In children and adolescents with sacroiliitis who have or are at risk for functional limitations, using physical therapy is conditionally recommended (PICO C.7).	Very low

* TNFi = tumor necrosis factor inhibitor (etanercept, adalimumab, infliximab, golimumab) (see Table 3 for other definitions).
† A bridging course of oral glucocorticoids was defined as a short course (<3 months) of oral glucocorticoids intended to control disease activity quickly during the initiation or escalation of therapy.

cervical spine, hip, and wrist), high disease activity, and/or for those judged by their physician to be at high risk of disabling joint damage. Of note, the majority of the Parent and Patient group voted against DMARDs as initial therapy, because a number of the participants had considerable adverse effects with methotrexate and had experienced better outcomes with biologics.

Subsequent therapy in patients with low disease activity (cJADAS-10 ≤2.5 and at least 1 active joint)

PICO B.5, B.6. *In patients with JIA and polyarthritis and low disease activity (cJADAS-10 ≤2.5 and at least 1 active joint) despite a DMARD or biologic, escalating therapy is conditionally recommended over no escalation of therapy*. This recommendation is conditional based on the very low quality of supporting evidence and parent and patient preferences regarding the risks and benefits of the treatment options. For this recommendation, escalating therapy is defined as any of the following: intraarticular glucocorticoid injection, increasing the DMARD or biologic dose (if not at optimal dosage), or changing biologic. Changing to an alternate DMARD (methotrexate) was suggested primarily for patients who had not yet received methotrexate and had not yet escalated to treatment with a biologic. Additional considerations included a degree of improvement while receiving current therapy

Table 6. Recommendations for the initial and subsequent treatment of children and adolescents with JIA and enthesitis*

Recommendation	Level of evidence
In children and adolescents with active enthesitis, NSAID treatment is ***strongly*** recommended over no treatment with an NSAID (PICO D.1).	Very low
In children and adolescents with active enthesitis despite treatment with NSAIDs:	
• Using a TNFi is conditionally recommended over methotrexate or sulfasalazine (PICO D.2, D.3).	Low
• Bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy is conditionally recommended (PICO D.4).† Bridging therapy may be of most utility in the setting of high disease activity, limited mobility, and/or significant symptoms.	Very low
Physical therapy	
• In children and adolescents with enthesitis who have or are at risk for functional limitations, using physical therapy is conditionally recommended (PICO D.5).	Very low

* TNFi = tumor necrosis factor inhibitor (etanercept, adalimumab, infliximab, golimumab) (see Table 3 for other definitions).
† A bridging course of oral glucocorticoids was defined a short course (<3 months) of oral glucocorticoids intended to control disease activity quickly during the initiation or escalation of therapy.

and the specific joint that was active. Synovitis preventing ambulation or otherwise interfering with important daily activities was identified as a factor that would guide more aggressive intervention (e.g., intraarticular glucocorticoid injection or adding/changing biologic).

Subsequent therapy in patients with moderate or high disease activity (cJADAS-10 >2.5)

PICO B.7. *In patients with JIA and polyarthritis and moderate or high disease activity despite DMARD monotherapy, adding a biologic to the original DMARD is conditionally recommended over changing to a second DMARD*. This recommendation was conditional based on the low quality of supporting evidence and parent and patient preferences regarding the risks and benefits of DMARDs and biologic medications (29,58,61,64,65,67,72–82).

PICO B.8. *In patients with JIA and polyarthritis and moderate or high disease activity receiving DMARD monotherapy, adding a biologic is conditionally recommended over changing to triple DMARD therapy*. The quality of evidence for this recommendation was low, based on the published pediatric trial being relatively small and not blinded (72). Although studies in RA have suggested that triple therapy is non-inferior to biologic therapy, the pediatric study showed improved outcomes for biologic therapy over triple DMARD therapy (83,84). This recommendation was also supported by Voting Panel concerns about adherence to the regimen and tolerability and parent and patient concerns about the burden of taking the 3 different medications.

PICO B.9. *In patients with JIA and polyarthritis and moderate or high disease activity receiving a first TNFi (with or without DMARD), switching to a non-TNFi biologic (tocilizumab or abatacept) is conditionally recommended over switching to a second TNFi*. This recommendation was conditional based on very low quality of supporting evidence and parent and patient preferences regarding the risks and benefits of biologics with different mechanisms of action (79,85). In making this recommendation, the Voting Panel also considered data from RA that have suggested better outcomes with switching to a non-TNFi biologic (86–88). The Voting Panel agreed that a second TNFi may be appropriate for patients who had a good initial response to their first TNFi (i.e., secondary failure), particularly failure due to the presence of suspected or measured antidrug antibodies to the first TNFi.

PICO B.10. *In patients with JIA and polyarthritis and moderate or high disease activity despite a second biologic, using a TNFi, abatacept, or tocilizumab (depending upon prior biologics received) is conditionally recommended over rituximab*. This recommendation was conditional based on very low quality of supporting evidence, Voting Panel member experience, and parent and patient preferences regarding the risks and benefits of biologics with different mechanisms of action. This recommendation was also supported by the availability of data from randomized clinical trials of tocilizumab and abatacept establishing their efficacy in JIA, which is lacking for rituximab (64,65,67). In addition, the article identified for the evidence report showed a higher rate of serious adverse events for rituximab compared to other biologics (78). The Voting Panel did discuss that rituximab may be considered earlier for RF-positive children based on data from RA, although the other 3 classes of biologics would still be primarily recommended (89).

Recommendations for the treatment of JIA and sacroiliitis (Table 5)

PICO C.1. *In children and adolescents with JIA and active sacroiliitis, treatment with an NSAID is **strongly** recommended over no treatment with an NSAID*. This recommendation was strong despite very low quality of supporting evidence in children, given the established utility of NSAIDs in adult spondyloarthritis and the analgesic effects of NSAIDs in children with other forms of arthritis. This recommendation is in alignment with the treatment recommendations for ankylosing spondylitis co-developed by the American College of Rheumatology/Spondylitis Association of America Spondyloarthritis Research and Treatment Network (32).

PICO C.2. *In children and adolescents with active sacroiliitis despite NSAIDs, adding a TNFi is **strongly** recommended over continued NSAID monotherapy*. Although the quality of supporting evidence in pediatrics for this recommendation was low, this recommendation is based on evaluation of both pediatric data and data from adult spondyloarthritis that include randomized controlled trials showing benefit (80,90–99).

PICO C.3. *In children and adolescents with active sacroiliitis despite NSAIDs, using sulfasalazine for patients who have contraindications to TNFi or have failed more than one TNFi is conditionally recommended*. This recommendation was conditional based on low quality of supporting evidence, particularly the relatively limited efficacy of sulfasalazine demonstrated in a randomized controlled trial in juvenile spondyloarthritis (100). However, it was considered as a potential option for patients with contraindications to TNFi and based on parent and patient considerations of the risks and benefits of biologics versus sulfasalazine. Sulfasalazine was also considered as an option for patients with adverse events associated with their initial TNFi that would be considered a class effect and who would therefore not be able to receive additional TNFi. Non-TNFi biologics

(e.g., interleukin-17 [IL-17] inhibitors) were not considered by the Voting Panel, because there are no published pediatric studies.

PICO C.4. *In children and adolescents with active sacroiliitis despite NSAIDs,* ***strongly*** *recommend against using methotrexate monotherapy*. Although the quality of supporting evidence for this recommendation was very low, this recommendation is based on data from adult spondyloarthritis suggesting lack of effectiveness (92,101–103). While we recommend against using methotrexate monotherapy as a treatment for sacroiliitis, methotrexate may have utility as adjunct therapy in patients with concomitant peripheral polyarthritis or to prevent the development of antidrug antibodies against monoclonal TNFi.

PICO C.5. *In children and adolescents with active sacroiliitis despite treatment with NSAIDs, bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy is conditionally recommended*. This recommendation is conditional based on very low quality of supporting evidence and known risks of glucocorticoid treatment. Bridging therapy with oral glucocorticoids may have the most utility in the setting of high disease activity, limited mobility, and/or significant symptoms.

PICO C.6. *In children and adolescents with active sacroiliitis despite treatment with NSAIDs, intraarticular glucocorticoid injection of the sacroiliac joints as adjunct therapy is conditionally recommended*. This recommendation was conditional based on very low quality of evidence and on varying parent and patient preferences regarding the procedure.

PICO C.7. *In children and adolescents with sacroiliitis who have or are at risk for functional limitations, using PT is conditionally recommended*. This recommendation was conditional based on the very low quality of supporting evidence and Voting Panel experience. It was also discussed that there may be a role for PT and activity modification in specifically identifying and reducing mechanical factors contributing to microtrauma and repetitive stress that could potentially contribute to disease activity in these patients (104).

Recommendations for the treatment of JIA and enthesitis (Table 6)

PICO D.1. *In children and adolescents with JIA and active enthesitis, NSAID treatment is* ***strongly*** *recommended over no treatment with an NSAID*. This recommendation is strong despite the very low quality of supporting evidence based on Voting Panel experience, established analgesic effects, and data from adult disease showing benefit (105).

PICO D.2, D.3. *In children and adolescents with JIA and active enthesitis despite treatment with NSAIDs, using a TNFi is conditionally recommended over methotrexate or sulfasalazine*. This recommendation is conditional based on the low quality of supporting evidence. While TNFi is preferred, the Voting Panel discussed that a trial of methotrexate or sulfasalazine may be warranted for patients with contraindications to TNFi, patients with mild enthesitis, and patients with concomitant active peripheral polyarthritis (80,90–95,100).

PICO D.4. *In children and adolescents with JIA and chronic active enthesitis despite treatment with NSAIDs, bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy is conditionally recommended*. This recommendation is conditional based on very low quality of supporting evidence and known risks of glucocorticoid treatment in the pediatric population. Bridging therapy with glucocorticoids may have most utility in the setting of high disease activity, limited mobility, and/or significant symptoms.

PICO D.5. *In children and adolescents with JIA and enthesitis who have or are at risk for functional limitations, using PT is conditionally recommended*. This recommendation was conditional based on very low quality of evidence and Voting Panel experience.

DISCUSSION

This guideline includes 39 recommendations for the treatment of children with JIA and non-systemic polyarthritis, sacroiliitis, and enthesitis. The quality of most of the available evidence was low or very low in relation to the relevant clinical PICO questions, resulting in 31 of the recommendations being conditional.

These recommendations provide an updated approach to the treatment of children with non-systemic polyarthritis, sacroiliitis, and enthesitis. These populations were chosen for this guideline because they have been the focus of significant recent research, with better delineation of the underlying biology and additional treatments available since the 2011 ACR recommendations for JIA. Similar to the 2011 recommendations, this guideline defined patient populations by clinical phenotypes rather than ILAR categories. This decision was made because data continue to suggest that current JIA categories may not accurately reflect the underlying biology and anticipated treatment responses in patients with juvenile arthritis.

This guideline differs from the 2011 recommendations in the definitions of risk factors and disease activity assessment used to generate patient scenarios. Although PICO questions were initially stratified by risk factors and disease activity, the Voting Panel ultimately determined that in most scenarios there were not sufficient data to recommend different treatments for these

patients, and recommendations were frequently combined. Another important difference from the 2011 recommendations is that initial NSAID monotherapy for polyarthritis is no longer recommended, given the established benefits of early initiation of DMARD treatment. Individual PICO questions for each biologic were initially considered but subsequently dropped by the Voting Panel, given mostly equivalent data for safety and efficacy between the biologics and lack of head-to-head comparisons. The exceptions were that TNFi are specifically recommended for sacroiliitis, and rituximab is considered only after TNFi, abatacept, and tocilizumab have been tried. This approach has resulted in a simplified treatment algorithm. Last, this guideline also includes recommendations for escalating care in the setting of low disease activity, highlighting the importance of achieving and maintaining complete disease control, which was not previously addressed.

The current recommendations also differ from the 2011 recommendations in that they were developed using GRADE methodology instead of the RAND/UCLA Appropriateness Method. The systematic, transparent, and explicit process of developing recommendations through GRADE is a major feature accelerating its adoption by professional groups internationally (www.gradeworkinggroup.org). Important features of this method are 1) specification of the patient groups, interventions, competing alternatives, and outcomes so that each recommendation is clearly focused on a particular clinical situation; 2) grading of the quality of evidence; and 3) basing the strength of recommendations on the quality of evidence, balance of benefits and harms, and patient values and preferences for different treatment options. This guideline considered parent and patient preferences assessed by a separate Parent and Patient Panel. Primary themes that emerged from that discussion were: 1) the importance of shared decision-making; 2) the importance of parents and patients receiving information regarding not only the preferred medication or intervention but also the alternatives; and 3) parent/patient support of earlier consideration of biologics given their experiences with decreased adverse effects and improved quality of life with the use of these medications relative to their experiences with methotrexate. Although this was a select group of parents and patients, and their experiences may not be representative of all patients, their discussion provided an important perspective that was incorporated into the Voting Panel discussion and voting.

A topic of particular debate among the Voting Panel was the appropriateness of the use of biologics as initial therapy in children with polyarthritis, particularly for those with risk factors. Ultimately, non–biologic DMARD therapy was recommended, but it was noted that there may be some patients for whom initial biologic therapy is indicated. This remains an area of active research, and currently ongoing studies may better clarify which patients are most likely to benefit from initial biologic therapy. Importantly, studies in pediatrics are underway or planned for a number of new medications, including JAK inhibitors and IL-17 and IL-12/23 inhibitors, and these medications may become useful additions as treatment options for JIA, particularly in patients with sacroiliitis for whom limited options exist. Other studies currently underway in parallel adult diseases may also inform the optimal treatment of enthesitis and the treatment of peripheral spondyloarthritis. Future guideline efforts may determine where these treatments fit into the treatment algorithm and will incorporate the results from the ongoing studies once complete.

Nonpharmacologic interventions addressed in this guideline included PT and OT. In each case, very limited data were identified, and future research in these modalities will be helpful in identifying patients most likely to benefit from these interventions and which modalities have most effectiveness for particular clinical scenarios.

The cJADAS-10 was used to provide general disease activity parameters for defining low and moderate/high disease activity. However, this is not intended to be prescriptive and should be interpreted within the overall clinical context. Furthermore, because the JADAS is a relatively new disease activity measurement tool, new cutoffs may be proposed, since additional data are generated that may accommodate different numbers of active joints or other levels of physician's or parent's global assessment. The identification of valid and practical disease activity measures in JIA remains an important research agenda in pediatric rheumatology. Nevertheless, it was agreed by the Voting Panel that treatment should be escalated in patients with even 1 active joint. Formal recommendations regarding disease activity measurement tools, cutoffs, and monitoring intervals were not specifically addressed in this guideline. Last, the management of inactive disease and the tapering and withdrawal of medications for patients with inactive disease are not addressed in this guideline but will be important for future guidelines.

Because the quality of evidence was overall low and most recommendations were conditional, clinicians, caregivers, and patients should use a shared decision-making process when considering these recommendations. While these recommendations are intended to address common clinical situations, all treatment decisions must be individualized, with consideration of the unique aspects of each patient's presentation, medical history, and preferences.

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EXTENDED REPORT

Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative

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ABSTRACT

Background In 2012, a European initiative called *S*ingle Hub and Access point for pediatric Rheumatology in Europe (SHARE) was launched to optimise and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and uveitis is possibly its most devastating extra-articular manifestation. Evidence-based guidelines are sparse and management is mostly based on physicians' experience. Consequently, treatment practices differ widely, within and between nations.

Objectives To provide recommendations for the diagnosis and treatment of JIA-associated uveitis.

Methods Recommendations were developed by an evidence-informed consensus process using the European League Against Rheumatism standard operating procedures. A committee was constituted, consisting of nine experienced paediatric rheumatologists and three experts in ophthalmology from Europe. Recommendations derived from a validated systematic literature review were evaluated by an Expert Committee and subsequently discussed at two consensus meetings using nominal group techniques. Recommendations were accepted if >80% agreement was reached (including all three ophthalmologists).

Results In total, 22 recommendations were accepted (with >80% agreement among experts): 3 on diagnosis, 5 on disease activity measurements, 12 on treatment and 2 on future recommendations.

Conclusions The SHARE initiative aims to identify best practices for treatment of patients suffering from JIA-associated uveitis. Within this remit, recommendations for the diagnosis and treatment of JIA-associated uveitis have been formulated by an evidence-informed consensus process to suggest a standard of care for JIA-associated uveitis patients throughout Europe.

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INTRODUCTION

In 2012, Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) was launched with the aim of optimising and disseminating diagnostic and management regimens for children and adolescents with rheumatic diseases. The European League against Rheumatism (EULAR) has produced a number of recommendations in the area of paediatric rheumatology such as juvenile dermatomyositis[1] using a standardised procedure[2] and referring to a generalised instrument for guideline assessment: the Appraisal of Guidelines for Research & Evaluation.[3]

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children, and uveitis is the most frequent and potentially most devastating extra-articular manifestation. There are no international consensus statements specifically relating to the diagnosis and treatment of JIA-associated uveitis although there are national guidelines from Germany and Spain.[4 5] Management is therefore based on physicians' personal experience; and considerable variation in clinical practice, both in terms of investigation and management of JIA-associated uveitis, was found in an extensive survey of uveitis experts.[6]

With the rapid development of novel therapies for JIA, clear recommendations based on available best evidence and expert opinion (when trial evidence is lacking) will help physicians in the care of patients with JIA-associated uveitis. The uveitis seen with JIA is usually chronic anterior uveitis which is asymptomatic, but acute anterior uveitis can also be seen in the enthesitis-related arthritis subtype.[7 8] There is a clear need to regularly update those managing patients with JIA uveitis through expert opinion. While the majority of treatments available for the treatment of arthritis have a solid evidence base from clinical trials, corresponding data for patients with uveitis may not be known or the level of evidence may not be as strong at the time of their introduction into clinical practice.

The primary aims of the recommendations forwarded by the Expert Group were to develop agreed strategies to

- prevent or reduce the likelihood of JIA-associated uveitis from occurring and minimise the damage at the time of diagnosis
- recommend treatments and management strategies that would reduce inflammation and prevent the development of those ocular complications most likely to cause irreversible visual loss.

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METHODS

A committee of 12 experts (AH, BV, CP, CE, SC-G, IF, JdB, JA, KW, RG, YU, NW) in paediatric rheumatology (n=9) or ophthalmology (n=3) was established to develop recommendations for JIA-associated uveitis based on consensus, but evidence informed, using EULAR standard operating procedures for developing best practice.[2 3]

Systematic literature search

The electronic databases PubMed/MEDLINE, Embase and Cochrane were searched independently by two researchers for eligible articles in February 2015. All synonyms of JIA were searched in Medical Subject Headings/Emtree terms, titles and abstracts (figure 1). Reference tracking was performed in all included studies (full search strategy is shown in figure 1). Experts (TC, AP, VB) selected papers relevant to uveitis associated with JIA investigations and/or treatment to be taken forward for validity assessment (inclusion and exclusion criteria shown in figure 1) by members of the expert committee.

Validity assessment

The selected articles were randomly allocated to the expert group, and two members per paper independently assessed the methodological quality of those papers meeting the inclusion

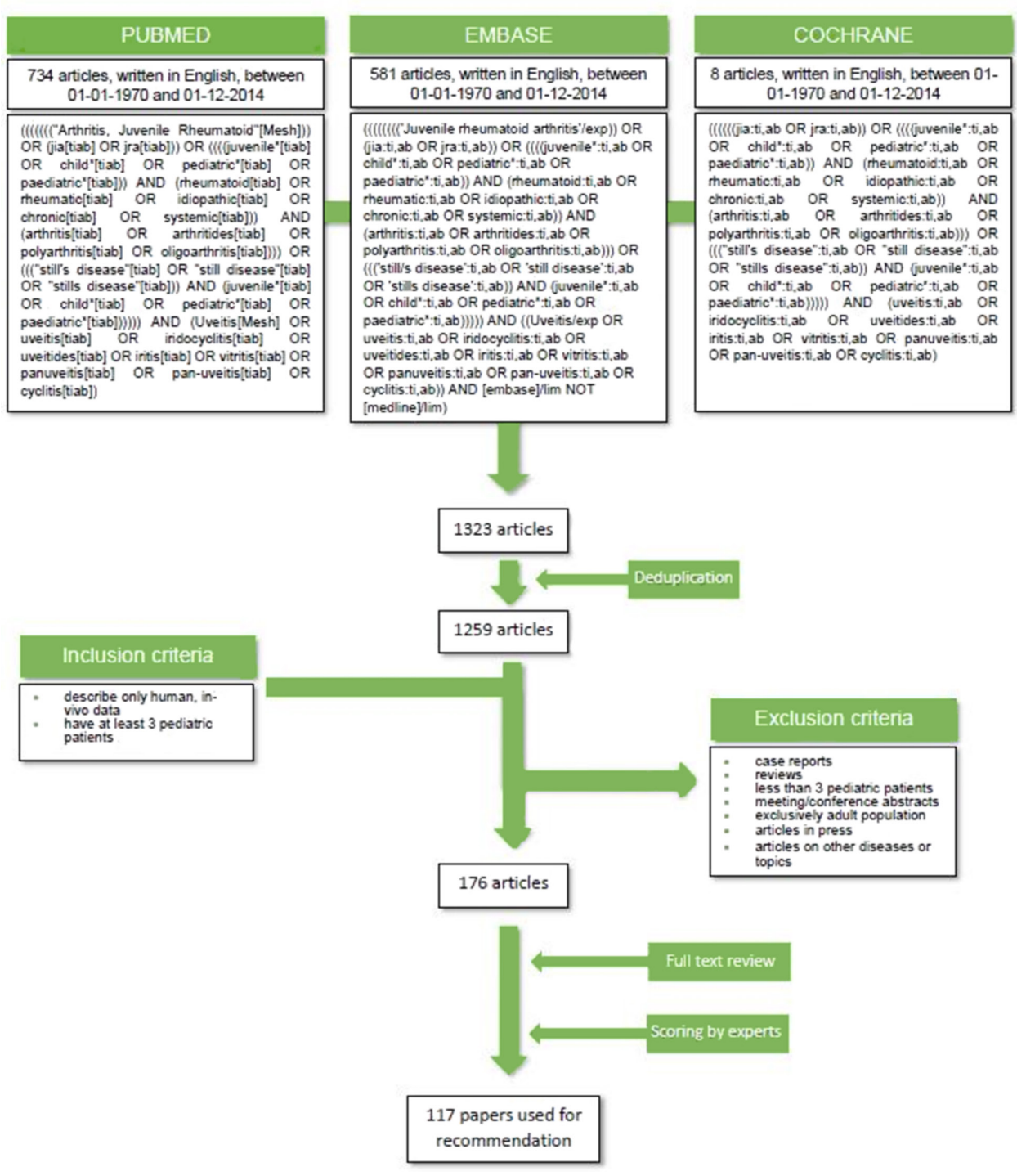
PUBMED
734 articles, written in English, between 01-01-1970 and 01-12-2014
((((((("Arthritis, Juvenile Rheumatoid"[Mesh])) OR (jia[tiab] OR jra[tiab])) OR ((((juvenile*[tiab] OR child*[tiab] OR pediatric*[tiab] OR paediatric*[tiab])) AND (rheumatoid[tiab] OR rheumatic[tiab] OR idiopathic[tiab] OR chronic[tiab] OR systemic[tiab])) AND (arthritis[tiab] OR arthritides[tiab] OR polyarthritis[tiab] OR oligoarthritis[tiab]))) OR ((("still's disease"[tiab] OR "still disease"[tiab] OR "stills disease"[tiab])) AND (juvenile*[tiab] OR child*[tiab] OR pediatric*[tiab] OR paediatric*[tiab])))))) AND (Uveitis[Mesh] OR uveitis[tiab] OR iridocyclitis[tiab] OR uveitides[tiab] OR iritis[tiab] OR vitritis[tiab] OR panuveitis[tiab] OR pan-uveitis[tiab] OR cyclitis[tiab])
EMBASE
581 articles, written in English, between 01-01-1970 and 01-12-2014
(((((((('Juvenile rheumatoid arthritis'/exp)) OR (jia:ti,ab OR jra:ti,ab)) OR ((((juvenile*:ti,ab OR child*:ti,ab OR pediatric*:ti,ab OR paediatric*:ti,ab)) AND (rheumatoid:ti,ab OR rheumatic:ti,ab OR idiopathic:ti,ab OR chronic:ti,ab OR systemic:ti,ab)) AND (arthritis:ti,ab OR arthritides:ti,ab OR polyarthritis:ti,ab OR oligoarthritis:ti,ab))) OR ((('still/s disease':ti,ab OR 'still disease':ti,ab OR 'stills disease':ti,ab)) AND (juvenile*:ti,ab OR child*:ti,ab OR pediatric*:ti,ab OR paediatric*:ti,ab))))) AND ((Uveitis/exp OR uveitis:ti,ab OR iridocyclitis:ti,ab OR uveitides:ti,ab OR iritis:ti,ab OR vitritis:ti,ab OR panuveitis:ti,ab OR pan-uveitis:ti,ab OR cyclitis:ti,ab)) AND [embase]/lim NOT [medline]/lim)
COCHRANE
8 articles, written in English, between 01-01-1970 and 01-12-2014
((((((jia:ti,ab OR jra:ti,ab)) OR ((((juvenile*:ti,ab OR child*:ti,ab OR pediatric*:ti,ab OR paediatric*:ti,ab)) AND (rheumatoid:ti,ab OR rheumatic:ti,ab OR idiopathic:ti,ab OR chronic:ti,ab OR systemic:ti,ab)) AND (arthritis:ti,ab OR arthritides:ti,ab OR polyarthritis:ti,ab OR oligoarthritis:ti,ab))) OR ((("still's disease":ti,ab OR "still disease":ti,ab OR "stills disease":ti,ab)) AND (juvenile*:ti,ab OR child*:ti,ab OR pediatric*:ti,ab OR paediatric*:ti,ab))))) AND (uveitis:ti,ab OR iridocyclitis:ti,ab OR uveitides:ti,ab OR iritis:ti,ab OR vitritis:ti,ab OR panuveitis:ti,ab OR pan-uveitis:ti,ab OR cyclitis:ti,ab)
1323 articles
Deduplication
1259 articles
Inclusion criteria
describe only human, in-vivo data
have at least 3 pediatric patients
Exclusion criteria
case reports
reviews
less than 3 pediatric patients
meeting/conference abstracts
exclusively adult population
articles in press
articles on other diseases or topics
176 articles
Full text review
Scoring by experts
117 papers used for recommendation

Figure 1 Summary of search strategy for identification of key articles.

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Table 1 Recommendations for diagnosis and screening in juvenile idiopathic arthritis (JIA)-related uveitis

Recommendation	L	S	Agreement (%)	References
1. All patients in whom a diagnosis of JIA is being considered should be screened for uveitis according to a contemporary and audited protocol. Formal screening protocol should be administered in all centres, where patients with JIA are seen.	2A	B	100	13–32
2. Frequency of ophthalmological follow-up visits must be based on disease severity and needs to be decided in conjunction with an expert ophthalmologist.	4	D	100	13–27 33–66
3. Patients with JIA stopping any systemic immunosuppressant are at risk of developing new onset uveitis or recurrence of uveitis after a prolonged remission. After stopping systemic immunosuppression, it is recommended that all patients with JIA are screened by an ophthalmologist at least every three months for at least 1 year.	2B	B	100	67–70

Agreement indicates the % of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of cohort studies; 1B, meta-analysis of case–control studies; 2A, cohort studies; 2B, case–control studies; 3, non-comparative descriptive studies; 4, expert opinion; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion. L, level of evidence; S, strength of evidence.

criteria (figure 1). Data were extracted using predefined scoring forms for diagnostic and therapeutic studies. Disagreements were resolved by discussion or by the opinion of a third expert. Adapted classification tables for diagnostic, therapeutic and epidemiological studies were used to determine the level of evidence and strength of each recommendation.[9–11]

Establishment of recommendations

As part of the EULAR standard operating procedure, experts described the main results and conclusions of each paper, along with their validity and level of evidence. These descriptions were collated by five experts (TC, GS, YU, RG, JdB) and used to formulate provisional recommendations which were reviewed by a panel of three experts (IF, NW, JdB). A summary of the evidence was presented along with each provisional recommendation to the expert committee. The recommendations were revised and discussed at a face-to-face meeting in March 2014 (Genova: 12 participants), using a Nominal Group Technique to reach a consensus.[12] A non-voting expert (AR) facilitated the process. Recommendations were accepted when ≥80% (10 of 12) of the experts agreed (including all three ophthalmologists).

RESULTS

Literature review

The literature search yielded a total of 1323 papers which, after deduplication, left 1259 unique articles. Evaluation of inclusion/exclusion criteria in titles and/or abstracts resulted in a core reference database of 176 articles for which full-text copies were obtained for quality screening by the expert committee. Of these, 117 were selected to support the development of consensus-based recommendations by the expert group (figure 1).

Recommendations

The sections that follow report the recommendations of the expert committee based on the supporting literature.[13–128] Tables 1–4 summarise the recommendations, the level of evidence that they provide and the strength of the recommendation, and the percentage of experts who agreed with these assessments.

Background

JIA is the most common chronic rheumatic disease in children with an incidence of 8.2 (7.5–9.0)/100 000 of the population under 16 and an annual prevalence of approximately 70.2 [16 – 140]/100 000.[129 130] The wide prevalence range has been attributed to the different study designs employed, but the incidence is thought to vary little worldwide.[130] The incidence of JIA-associated uveitis is thought to be approximately 1/10 000 and there is some evidence that it is less frequent in oriental populations with JIA.[7 131]

Structural complications, some of them leading to irreversible visual loss, include cataracts, glaucoma, band keratopathy, macular oedema, retinal detachment and sequelae associated with chronic hypotony. The uveitis usually has an insidious time course and can be chronic or recurrent but, most frequently, JIA-associated uveitis is a chronic relapsing condition lasting several years. It almost universally starts as an anterior uveitis, but in rare instances can become a panuveitis. JIA-associated uveitis is usually asymptomatic in the age group in which it

Table 2 Recommendations for disease activity measurement in juvenile idiopathic arthritis (JIA)-related uveitis

	L	S	Agreement (%)	References
4. There should be good communication between the ophthalmologist and the paediatric rheumatologist concerning changes in disease activity treatment changes and responsibility for treatment monitoring.	3	C	100	71
5. There is a need to develop shared outcome measures to help guide decisions on systemic treatment.	4	D	100	
6. At present, there is no validated biomarker to follow the activity of uveitis.	2A	B	100	4 21 29 31 32 37 41 46 72–76
7. At present, no widely accepted definition of inactive disease for JIA-related uveitis is available. The goal of treating JIA-associated uveitis should be no cells in the anterior chamber. The presence of macular and/or disk oedema, ocular hypotony and rubeosis iridis may require anti-inflammatory treatment even in the absence of AC cells.	2B	B	100	4 69 78
8. We recommend 2 years of inactive disease off topical steroids before reducing systemic immunosuppression (both DMARDs and biological therapies).	3	C	92	67

Agreement indicates the % of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of cohort studies; 1B, meta-analysis of case–control studies; 2A, cohort studies; 2B, case–control studies; 3, non-comparative descriptive studies; 4, expert opinion; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion. DMARD, disease-modifying anti rheumatic drugs; L, level of evidence; S, strength of evidence.

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Table 3 Recommendations for treatment in juvenile idiopathic arthritis (JIA)-related uveitis

	L	S	Agreement (%)	References
9. Active uveitis in JIA usually requires immediate treatment.	2B	B	100	69 71 78–80
10. Topical corticosteroids (preferably prednisolone acetate or dexamethasone) are the first-line treatment of anterior uveitis.	4	D	100	81
11. Topical and systemic NSAIDs have no demonstrable effect as monotherapy, but may be used as additional therapy.	3	C	92	79 81 82
12. Systemic immunosuppression in active uveitis is recommended if poor prognostic factors are present at the first visit. Poor prognostic factors including lack of remission later on during the disease course require systemic immunosuppression.	2A		100	4 19 22 29 55 56 65 78 83 84
13. Systemic immunosuppression is recommended if inactivity could not be reached within 3 months or inflammation is reactivating during steroid dose reduction.	2B	B	100	55 59 68 69 78 80 85–87
14. Methotrexate is the first choice as systemic immunosuppression.	4	D	100	68 84 88–95
15. In case of methotrexate inefficacy or intolerance, adding or switching to biological treatment is recommended.	3	C	92	91–104
16. The use of anti-TNF treatment strategies *(adalimumab>infliximab>golimumab)* is recommended in patients with uveitis refractory/resistant to DMARD therapy, principally methotrexate.	3	C	100	86 100 101 104–117 120–124 126 127
17. Based on the current evidence, etanercept should not be considered for JIA-associated uveitis.	1B	A	100	87 100 109 117–121
18. Switching between different anti-TNF treatments might be valuable if uveitis is refractory to the first anti-TNF, even though the present evidence comes from small case series or inception cohorts.	3	C	100	87 113 116 122
19. In case of lack of efficacy, consider testing for antidrug antibodies and drug trough level. If the patient has no antibodies but has low trough levels, consider increasing the dose or shortening the interval.	4	D	100	
20. Tocilizumab, rituximab and abatacept might be potential options for cases refractory to previous anti-TNF therapy.	3	C	100	123–125

Agreement indicates the % of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of cohort studies; 1B, meta-analysis of case–control studies; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4, expert opinion; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion.; DMARD, disease-modifying antirheumatic drugs; L, level of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; S, strength of evidence; TNF, tumour necrosis factor.

most commonly develops (age 3–7 years), but severe inflammation may cause symptomatic pain and redness and these symptoms and signs, as well as pupil distortion, may be noticed by carers and lead to early referral. Reduced visual function is an uncommon cause of presentation in small children unless it is severe and usually secondary to irreversible structural damage. The presence of antinuclear antibodies (ANA), oligoarthritis and early onset of arthritis are predominant risk factors for chronic anterior uveitis in those with JIA, and improved identification of children at risk is a key priority for targeted screening programmes. This exercise only looked at chronic anterior uveitis associated with JIA and not at acute anterior uveitis seen in human leukocyte antigen (HLA) B27-positive children with enthesitis-related arthritis.

Table 4 Recommendations for future plans in juvenile idiopathic arthritis (JIA)-related uveitis

	L	S	Agreement (%)	References
21. Validated outcome measures for JIA-associated uveitis are needed	3	C	100	73 126–128
22. Controlled clinical trials are needed for JIA-associated uveitis	1B	A	100	119

Agreement indicates the % of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of cohort studies; 1B, meta-analysis of case–control studies; 2A, cohort studies; 2B, case–control studies; 3, non-comparative descriptive studies; 4, expert opinion (diagnostic studies); 1A, meta-analysis of randomised controlled trials; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4, expert opinion (therapeutic studies); A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion. , level of evidence; S, strength of evidence .

Timely and aggressive treatment is clearly needed where there is significant damage at the time of diagnosis. However, the variable course of the disease means that some significant events may occur years after therapy commences and there remains considerable disagreement among expert practitioners about the timing and indications for treatment escalation.[132 133]

Recommendations for diagnosis and screening in JIA-related uveitis

Screening for JIA-associated uveitis

All patients with JIA should be screened for uveitis according to contemporary and audited screening protocols which should be implemented in all centres in which patients with JIA are being managed.[42 43] There is no necessity for the screening process to take place in the same institution as the rheumatological care. It is especially important, however, that all children in whom the diagnosis of JIA is being considered should have a timely check by a local ophthalmologist rather than wait for confirmation of the diagnosis from a paediatric rheumatology referral centre. It is the responsibility of paediatric rheumatologist to ensure children with JIA are referred for screening. Screening starts with all individuals with a 'suspected' diagnosis of JIA and the clinical responsibility for organising this service needs to be clear. This is independent of whether it is the remit of the ophthalmologist not specialised in uveitis, paediatrician or rheumatologist (table 1). The evidence published to suggest that the risk factors originally proposed for the development of chronic uveitis in the JIA population (early-onset arthritis, ANA positivity and oligoarticular subtype) is suboptimal: the expert group noted that despite the fact that a number of screening protocols have been published there is no evidence to suggest that any one of them is superior.[5 23 26 61 74]

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Advances in genetics have not found any more specific diagnostic markers than the HLA types originally reported as being associated with both oligoarticular disease and uveitis.[14 15 30 32 38 48 50 56] There is no evidence, at present, that genotyping adds specificity to the established clinical risk factors on which contemporary screening programmes are based.

Despite the advances in subtyping ANAs in other rheumatic disorders, there has been little advance in our understanding of the association of ANAs with the risk of JIA-associated uveitis[28 34 35 41 60 67] although antibodies to nuclear structures such as histones and chromatin[16 21 41 52–54 64 77] and ocular antigens have been reported.[13 33 51 75] Two studies found that children with higher inflammatory activity (as determined by higher erythrocyte sedimentation rate (ESR) values) when oligoarthritis or polyarthritis was diagnosed had an increased risk of developing uveitis.[27 31]

There is a clear unmet need to adapt screening policies to the contemporary usage of early systemic immunosuppressant treatment of arthritis[57 61 62 64] and novel biomarkers and future genotyping may improve targeting of the population being screened.

Monitoring during follow-up

The risk of visual symptoms and potential for relapse in patients initially responding to treatment highlights the necessity for maintained regular close ophthalmological scrutiny. The expert group recommended that the frequency of ophthalmological follow-up should be based on ocular disease severity and decided upon in conjunction with an expert ophthalmologist.

Screening after stopping treatment of uveitis

Methotrexate (MTX) is the immunosuppressive therapy of choice in patients with JIA-related uveitis (see recommendation 14, table 3). Once long-lasting remission of uveitis is achieved, MTX is usually stopped, but the optimal period of disease control prior to withdrawal of both topical and systemic treatment remains unclear. Patients stopping MTX are at risk of developing new onset uveitis or recurrence of uveitis after prolonged remission in the first year. Indeed, the majority of patients in a recently reported series relapsed within 24 months of stopping therapy.[67–70] Consequently, after stopping immunosuppression with MTX (prescribed for arthritis or uveitis) it is recommended that all patients with JIA are screened by an ophthalmologist at least every three months for a minimum of 1 year.

It also remains unclear for those patients on multiple treatments, in which order treatments are best withdrawn. Relapse of uveitis after withdrawal of MTX appears to be delayed in older patients, those who have been on treatment for longer duration.[67] The authors recommended that the period of uveitis inactivity should be >2 years before MTX is withdrawn.[67] The expert group also recommend that patients should have 2 years of inactive disease while not using topical steroids before reducing systemic immunosuppression.

There is a clear need for continuing monitoring in the early period of remission after medications are stopped, especially in patients on long-term therapy, topical or systemic, which had maintained disease control. The expert group recommends that monitoring of disease in remission by an ophthalmologist should be at least every three months and should continue for at least 3 years off all forms of treatment. The length of remission best predicting lifetime remission remains unknown. More robust data on effective screening strategies are required.

Recommendations for disease activity measurement in JIA-associated uveitis

A pivotal goal in the management of JIA-associated uveitis is to minimise loss of vision through the early diagnosis of ocular morbidity. Early referral and appropriate treatment to eliminate ocular inflammation are seen to be crucial in preserving visual acuity. Visual loss is mainly caused by glaucoma, macular damage from inflammatory oedema, hypotony or amblyopia: structural damage can occur prior to diagnosis and also arise following years of poorly controlled inflammation.

Multiple studies have found delayed presentation with damage at diagnosis, surgery and length of follow-up to be the major risks for lifelong visual loss.[4 68 78] Male gender and non-Caucasian race may be additional risk factors for some complications.[18 19 37 56 65 71] Immunosuppressive treatment is therefore aimed at reducing agreed measures of active intraocular inflammation which include the level of cellular infiltrate, breakdown of vascular barriers (eg, flare) and macular oedema: few of these measures have been validated and different markers may be appropriate in eyes with different levels of structural damage or at different stages of disease.[134]

In one study, an increase in anterior chamber cell grade was associated with elevated rates of visual loss in a dose-dependent fashion, whereas immunotherapy was associated with a reduced risk of visual loss, particularly for the 20/50 or worse outcome (HR 0.40; P<0.01).[78] Others have found anterior chamber flare a better predictor of visual loss.[63]

There are no established biomarkers currently available for predicting disease activity or guiding treatment in JIA-associated uveitis and research efforts in this area need to be intensified (table 2).[24 32 34 35 40 44 49 75–80]

In a small group of children with JIA-related anterior uveitis, serum interleukin-2R levels were significantly increased,[72] while in a larger cohort of children there was a significant correlation between the presence of anterior uveitis and aqueous humour levels of transthyretin.[73] Until reliable biomarkers are found, management relies on frequent ophthalmic examination. Future opportunities might include gene expression and proteomic profiling of the serum, peripheral blood leucocytes and aqueous humour; measurement of acute-phase reactants; HLA typing and determination of ANAs.[74] Evidence-based guidelines by the German Ophthalmological Society, the Society for Childhood and Adolescent Rheumatology and the German Society for Rheumatology noted that macular oedema, ocular hypotony and rubeosis iridis are often associated with chronic inflammation and anti-inflammatory treatment should be initiated (or intensified) even in the absence of cells in the anterior chamber.[4] The expert group recommended that the goal of treating JIA-associated uveitis should be no cells in the anterior chamber although this may not be practically possible (table 2). With reference to the Standardization of Uveitis Nomenclature (SUN) Working Group, a multinational interdisciplinary group (MIWGUC) developed a set of core outcome measures for uveitis that may provide a framework for evaluating disease severity and its course, risk for structural impairment, levels of impairment in visual function and responses to treatment.[74] These would be invaluable in clinical studies involving patients with JIA-associated uveitis. However, these proposed outcome measures remain to be validated in children.[135] To best guide treatment decisions, there should be good communication between the ophthalmologist and the paediatric rheumatologist concerning changes in disease activity treatment changes and responsibility for treatment monitoring. Recently published guidance for management

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of non-infectious uveitis in adults has some important principles for the management of panuveitis in all age groups.[136]

Recommendations for treatment in JIA-associated uveitis

Active uveitis in JIA usually requires immediate treatment. In a comparison of two cohorts of patients with new-onset JIA, separated by a 10-year interval, the more recently treated patients received early intensive treatment and close monitoring, and reported fewer complications and milder uveitis with visual loss avoided in most cases.[80] Treatment factors reported to be associated with improved outcomes included introduction of immunosuppressive therapy earlier in the course of the disease or at a younger age[69] and treatment with immunosuppressants generally.[71 78]

Based on past usage, the expert group recommend that topical corticosteroids (preferably prednisolone or dexamethasone) are the first-line treatments of choice for both acute and chronic anterior uveitis.[4 5 81 129] Children with JIA-related uveitis are frequently treated with topical corticosteroids over extended periods, and this increases the risk of cataract formation and glaucoma.

One study found that the increased risk of cataract formation with high-dose topical steroids was independent of active uveitis or presence of posterior synechiae.[81] The risk increased as the number of drops of topical corticosteroids instilled increased. The data suggested that patients may be treated with low doses of topical corticosteroids (≤3 drops daily) over moderate periods of follow-up (median 4 years; range 0.5–15 years) with a low risk of developing cataracts.[81] Among eyes receiving ≤2 drops daily, the incidence of cataract was 0/eye year. There appears to be no evidence to suggest that less potent topical steroids reduce adverse effects in this patient population (table 3). Systemic corticosteroids are not usually preferred in children due to risks of growth suppression and osteopenia; however, they are potentially helpful in individual cases for rapid control of severe uveitis or in the presence of macular oedema.

In a retrospective study, the adjunctive use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of chronic iridocyclitis was evaluated in 14 patients, 8 with JIA and 6 with idiopathic iridocyclitis.[82] In all patients, the activity of the iridocyclitis improved with the addition of NSAIDs to their treatment regimens, permitting reduction in the dose of corticosteroid drugs. These data suggest that NSAID therapy may have an adjunctive role in the treatment of chronic iridocyclitis in childhood, but not as monotherapy.

Systemic immunosuppression for active uveitis is recommended to reduce complications in those cases where topical steroids are insufficient to eliminate ocular inflammation short term, or such high doses are required that treatment risks outweigh the beneficial effects. However, the threshold for introducing systemic treatment is lower in those with multiple risks for visual loss as discussed earlier.[129] Immediate systemic immunosuppression in active uveitis is recommended if poor prognostic factors are present at the first visit. Studies suggest instituting aggressive immunosuppression in high-risk patients even before there is any clear evidence of complications developing.[27 39] Poor prognostic factors include uveitis antedating arthritis[19 22 74]; posterior synechia[55 68 74 75]; male gender[19 22 55]; band keratopathy, glaucoma and cataract[55]; poor initial vision, hypotony, macular oedema and dense vitreous body opacification[55]; and lack of remission later on during the disease course (table 3). Age at the time of uveitis onset does not appear to be a risk factor.[22 56]

Definition of treatment failure

Treatment failure should lead to a change in treatment dose, route or modality taking into consideration the fact that many of the drugs require different times to achieve their optimal effect and there are sometimes only a limited number of drugs available. Inappropriate drug changes may result from difficulties in achieving consensus on the definition of treatment failure. In a retrospective study, the clinical outcome of 23 patients with JIA-associated uveitis unresponsive to corticosteroids was ascertained. Uveitis was controlled using immunosuppressive therapy in all cases.[86] Patients treated within 4–30 months from onset of uveitis achieved better improvement of vision compared with patients who received immunosuppressive therapy after 3 years ($P<0.005$ for right and left eyes pooled; $P=0.0075$ for best eyes; $P=0.0375$ for worst eyes). These data are supported by findings from the SITE study which reported that among patients with JIA-associated uveitis receiving tertiary care use of immunosuppressants reduced the risk of vision loss by about 60%.[78] The expert group recommended that systemic immunosuppression should be used if inactivity cannot be achieved with topical steroids within 3 months or inflammation is reactivated during steroid dose reduction. The benefits of immunosuppressive therapy are now well recognised, and, in general, patients in remission received this treatment earlier in the course of disease compared with patients who relapsed.[55 59 68 78–87]

Based on findings of efficacy and tolerability/safety from a number of studies, the expert group recommended that MTX is the immunosuppressive therapy of choice in patients with JIA-related uveitis.[68 84 88–90] Other forms of immunosuppressive therapy such as azathioprine, sulfasalazine, mycophenolate mofetil, cyclosporine and leflunomide have been assessed in patients with uveitis, often in MTX-resistant cases.[91 95] The studies have generally included a small numbers of patients, and in the case of cyclosporine, the clinical efficacy was poor and the authors noted that it has limited value in this indication.[94] The results with other forms of immunosuppressive therapy were more encouraging, but were in fewer patients.[91–93 95] At this stage they may prove to be useful treatment options in patients not responding to, or who cannot tolerate, MTX and they also have a place accompanying biological treatment in those who are MTX-intolerant. There is also evidence of the greater effectiveness of MTX in controlling arthritis in JIA compared with other conventional immunosuppressants. It is not uncommon for treatment to fail when treatments other than MTX are used because of recurrent arthritis rather than failure to control the uveitis.

As noted above, the evidence with other forms of immunosuppressive therapy in patients with JIA-related uveitis is low,[91–95] whereas many conventional immunosuppressants are used in adult onset uveitis with no specific agent favoured as the first choice. In both adult and childhood patients who fail to respond to conventional immunosuppressants, expert groups recommend adding or switching to biological treatments. There is a growing number of studies supporting the use of biological therapy in MTX refractory uveitis.[93–108] A wide range of biological therapies have been investigated in JIA-related uveitis refractory to conventional therapy, with adalimumab being the most widely studied; other agents investigated include infliximab, daclizumab, etanercept, golimumab, abatacept, tocilizumab and rituximab.[96–108 123–125]

All of the biological therapies investigated produced some benefit in patients with uveitis refractory to conventional therapy.[86 100–127] There are very few comparative studies. One

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study found infliximab to be significantly superior to etanercept in children with refractory JIA-associated chronic uveitis.[100] In another small study, adalimumab was more efficacious than infliximab when used as first-line anti-TNF treatment.[106] Adalimumab also produced higher remission rates versus infliximab in the medium-term treatment (at least 12 months) of patients with JIA-related uveitis[107] and in children with uveitis it was significantly superior to infliximab in maintaining remission over a 3-year treatment period.[102] The expert group recommends treatment with anti-tumour necrosis factor (TNF) agents (adalimumab>infliximab>golimumab) in patients with uveitis refractory/resistant to disease-modifying antirheumatic drug (DMARD) therapy, principally methotrexate.[86 100–127]

The use of TNF inhibitors in uveitis was hypothesised based on their proven efficacy in a range of systemic inflammatory disorders including JIA, rheumatoid arthritis and Crohn's disease.[109] Etanercept is a recombinant DNA dimeric fusion protein that antagonises TNF-α, and it has proven to be effective in children with polyarticular JIA.[118] Evidence for the clinical benefit of etanercept in uveitis has generally been disappointing; it was associated with a high relapse rate and a high risk for developing uveitis flares.[87 100 109 117–121] Based on these findings, the expert group recommend that etanercept should not be considered for JIA-associated uveitis.

Findings from studies including small numbers of patients provide evidence that if treatment with one anti-TNF agent becomes ineffective switching to a different anti-TNF agent could prove to be clinically beneficial.[87 113 116 122] The efficacy and safety of adalimumab was evaluated in in 26 children with JIA resistant to current therapy (disease-modifying drugs in 17 cases and anti-TNF agents in 9 cases). Switching to adalimumab had a beneficial impact on disease control in 17 (65.4%) of patients.[113] In total, 17 patients with severe recalcitrant uveitis (resistant to etanercept, infliximab, adalimumab, rituximab or abatacept) were switched to golimumab and 14 achieved a positive response, and in 12 of these the disease was inactive at the final visit (mean duration 22 months; range 6–29 months).[116] Dhingra *et al* reported preliminary evidence that in seven cases of refractory uveitis switching between biological agents (over a period of 5–24 months) helped to control intraocular inflammation.[122]

While the literature search revealed no direct evidence of the effects of low drug trough levels or the development of anti-drug antibodies (ADAs) on the clinical efficacy of biological agents in patients with uveitis, the expert group considered findings from other clinical settings. They concluded that in cases of loss of efficacy over time consideration should be given to testing for ADAs and drug trough levels.[137 138] If the patient has no antibodies, but has low trough levels, increasing the dose or shortening the interval may be an option.[139]

In keeping with an earlier recommendation (18, table 3), there are data from small studies that in patients with JIA-related uveitis

Table 5 Proposed domains and items for outcome measures of juvenile idiopathic arthritis (JIA)-associated uveitis (from the Multinational Working Group in JIA-related uveitis)[74]

Domains	Items
Grade of cells in anterior chamber	Slit-lamp examination (according to SUN criteria)
Grade of flare in anterior chamber*	Slit-lamp examination for routine clinical practice and prospective trials (according to SUN criteria) Laser flare photometry for prospective trials
Number of visits with active uveitis	Records of treating physician ► Duration of activity over a minimum of four visits/year
Visual acuity (appropriate test for age)	Best-corrected visual acuity Thresholds: ≤20/50, ≤20/200 and no light perception Estimate contribution of amblyopia, yes/no
Development of structural complications	Synechiae, yes/no ► Initial and additional Ocular hypotony, yes/no (<5 mm Hg) Ocular hypertension, yes/no (>21 mm Hg) Glaucoma, yes/no Cataract, yes/no Band keratopathy in the central cornea, yes/no Macular oedema by optical coherence tomography, yes/no ► Funduscopy and optical coherence tomography for routine clinical practice (for macula and optic disc) ► Funduscopy and optical coherence tomography for prospective trials Epiretinal membrane formation, yes/no ► Funduscopy for routine clinical practice ► Funduscopy and optical coherence tomography for prospective trials
Quality of life	Childhood Health Assessment Questionnaire Child Health Questionnaire Pediatric Quality of Life Inventory Uveitis-specific quality of life instrument (not yet available for non-English speaking countries)
Overall uveitis-related disability	Assessment by parents, visual analogue scale Assessment by children, visual analogue scale Assessment by treating ophthalmologist, visual analogue scale Assessment by treating paediatric rheumatologist, visual analogue scale
Social outcome	School/kindergarten absence
Anti-inflammatory medication*	Reduction of corticosteroid dose—topical dose—systemic dose
Surgery*	Yes/no
Biomarkers	Research tools (not currently available

*Not an outcome measure, but should be documented.
SUN, Standardization of Uveitis Nomenclature.

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refractory to conventional therapy and at least one anti-TNF therapy switching to drugs such as abatacept, rituximab or tocilizumab may be beneficial.[123–125] This included patients in whom the main cause of poor visual acuity was macular oedema.[125] There is now growing evidence for the role of tocilizumab in macular oedema associated with uveitis.[140 141] There is also an ongoing trial of tocilizumab in children with anti-TNF refractory JIA-associated uveitis (http://www.aptitude-trial.org.uk/).

The optimum time for surgery in children with complications from refractory uveitis has not been addressed as a recommendation due to paucity of evidence. Recent literature does demonstrate that a significant number of children with uveitis still require surgery for complications.[142]

Recommendations for future plans in JIA-related uveitis

A MIWGUC identified the need for clinical trials and longitudinal studies to determine the benefits and costs of health interventions in this setting.[74] To achieve this the group proposed a core set of outcomes aimed at ensuring that changes in relevant outcomes were measured, and that standardisation of outcome measures would facilitate data pooling and comparisons between interventions (tables 4 and 5). The outcomes should be agreed on by both researchers and patients, and they will provide a common focus for interventional studies. Disease-specific and universally agreed on validated outcomes are likely to reduce selective reporting and reporting bias.[74] A limitation of this core set of outcomes is that, despite the fact that there was consensus by the Working Group regarding their utility, they still remain unvalidated. Visual impairment has a significant impact on the quality of life (QOL) of patients with JIA-related uveitis and vision-related QOL relates to the degree to which vision impacts the individual's ability to perform activities of daily living as well as social, emotional and economic well-being.[126–128] The Effects of Youngsters' Eyesight QOL is a useful instrument for measuring the effects of uveitis on QOL which is currently being validated.

The expert group indicated a need for more well-controlled clinical trials in children with JIA-related uveitis to provide the scientific best evidence in the areas of diagnosis, screening, disease activity and treatment to enable the optimal care of these patients.

DISCUSSION

Following a systematic review of the literature and Nominal Group Technique methodology, under the auspices of SHARE and EULAR operating procedures, 22 recommendations for the screening, diagnosis, disease activity monitoring, treatment and future plans for children with JIA-associated uveitis were accepted with at least 80% agreement. In a disease setting where the evidence base is limited by small numbers of patients, and which is developing rapidly, these expert recommendations should help specialists with the evidence-based advice to provide optimal care for their patients.

It should be noted that, in general, the level of evidence was quite low with 13 of 22 recommendations being level 3 or 4, seven level 2 and only two level 1. This highlights the need for more research in this clinical setting where a number of new therapies, particularly biological agents, have been introduced in recent years. At the time that the data search for this article took place, the expert group noted a need for more well-controlled clinical trials in children with JIA-related uveitis. The goal being to ensure that scientific best evidence is used to support optimal treatment. In the interim period, but clearly outside the search time frame of this review, a well-designed randomised controlled trial (RCT) has been published which compared adalimumab with placebo in children with JIA-related uveitis who were taking a stable dose of MTX.[135] Active treatment was shown to control inflammation and was associated with a lower rate of treatment failure compared with placebo. These results do not alter the recommendations of the expert group, but reinforce the intent of recommendation 15 in table 3: 'In case of methotrexate inefficacy or intolerance, adding or switching to biological treatment is recommended'. The only difference being that this recommendation is now supported by level 1 evidence, rather than level 3 evidence. More recently, another smaller RCT of adalimumab has also been published showing efficacy of adalimumab in JIA–uveitis although this study used flare as the primary outcome measure.[143] The utility of biological therapies is receiving wider attention, for example, a number of studies have reported the benefits of tocilizumab.[141 144] These findings from outside the systematic data search time period emphasise the need to regularly update the recommendations of the JIA-associated uveitis expert group so as to provide the highest levels of care in this clinical setting.

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Classification criteria for autoinflammatory recurrent fevers

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ABSTRACT

Background Different diagnostic and classification criteria are available for hereditary recurrent fevers (HRF)—familial Mediterranean fever (FMF), tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), mevalonate kinase deficiency (MKD) and cryopyrin-associated periodic syndromes (CAPS)—and for the non-hereditary, periodic fever, aphthosis, pharyngitis and adenitis (PFAPA). We aimed to develop and validate new evidence-based classification criteria for HRF/PFAPA.

Methods Step 1: selection of clinical, laboratory and genetic candidate variables; step 2: classification of 360 random patients from the Eurofever Registry by a panel of 25 clinicians and 8 geneticists blinded to patients' diagnosis (consensus ≥80%); step 3: statistical analysis for the selection of the best candidate classification criteria; step 4: nominal group technique consensus conference with 33 panellists for the discussion and selection of the final classification criteria; step 5: cross-sectional validation of the novel criteria.

Results The panellists achieved consensus to classify 281 of 360 (78%) patients (32 CAPS, 36 FMF, 56 MKD, 37 PFAPA, 39 TRAPS, 81 undefined recurrent fever). Consensus was reached for two sets of criteria for each HRF, one including genetic and clinical variables, the other with clinical variables only, plus new criteria for PFAPA. The four HRF criteria demonstrated sensitivity of 0.94–1 and specificity of 0.95–1; for PFAPA, criteria sensitivity and specificity were 0.97 and 0.93, respectively. Validation of these criteria in an independent data set of 1018 patients shows a high accuracy (from 0.81 to 0.98).

Conclusion Eurofever proposes a novel set of validated classification criteria for HRF and PFAPA with high sensitivity and specificity.

Key messages

What is already known about this subject?
- Hereditary recurrent fever (HRF) syndromes are genetic disorders secondary to mutations in genes involved in the innate immune response.
- A number of classification or diagnostic criteria have been developed in the past.
- Overall, these criteria lack accuracy and do not consider the results of genetic analyses, now an essential tool for the accurate diagnosis and classification of HRF.

What does this study add?
- We developed and validate new evidence-based classification criteria for HRF and periodic fever, aphthosis, pharyngitis and adenitis, combining international expert consensus, statistical evaluation of real patients from a large data set of patients in the Eurofever Registry.
- The new classification criteria combine for the first time clinical manifestations with genotype.

How might this impact on clinical practice or future developments?
- The use of these classification criteria is recommended for inclusion of patients in translational and clinical studies, but they cannot be used as diagnostic criteria.

INTRODUCTION

In the last 20 years the discovery of the inflammasome and the related genes of the now called systemic autoinflammatory diseases (SAIDs) has led to a completely new line of research. SAIDs are caused by exaggerated activation of the innate immune system, in the absence of high-titre autoantibodies or antigen-specific T-cells.[1 1] Recurrent (or periodic) fevers are characterised by inflammatory flares separated by intervals of general overall well-being. Some conditions are caused by a genetic defect and are collectively referred to as hereditary recurrent fever (HRF). Familial Mediterranean fever (FMF) is caused by mutations of *MEFV*[2 3];

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mevalonate kinase deficiency (MKD), by mutations of the mevalonate kinase gene (*MVK*)[4 5]; tumour necrosis factor (TNF) receptor-associated periodic fever syndrome (TRAPS), by mutations of type I TNF receptor (*TNFSRF1A*)[6]; and cryopyrin-associated periodic syndromes (CAPS), by mutations of *NLRP3*.[7 8] More common forms of recurrent fever syndromes include periodic fever, aphthosis, pharyngitis and adenitis (PFAPA) syndrome, which is a multifactorial disorder.[9] So far, several clinical diagnostic and classification criteria have been proposed for HRF[10–15] and PFAPA.[9 16] Overall, these criteria lack accuracy and do not consider the results of genetic analyses, now an essential tool for the accurate diagnosis and classification of HRF.

This distinction between classification and diagnostic criteria is not always clear in clinical practice, and the two terms are often (wrongly) used interchangeably.[17] Classification criteria facilitate accurate identification of diseases for clinical or epidemiological studies, in this context reliably differentiating one autoinflammatory disease from another, but are not designed to diagnose that autoinflammatory disease; hence, classification criteria make the assumption that important disease mimics (eg, chronic infection or malignancy) have already been excluded. In contrast, diagnostic criteria are designed to positively rule in a specific diagnosis in an individual patient, while excluding all conditions with different overlapping disease manifestations based on derivation and validation in cohorts that include important disease mimics. As such, classification criteria cannot be used as diagnostic criteria.[18 19] The purpose of this study was to develop and validate new evidence-based classification criteria for HRF and PFAPA, combining international expert consensus and statistical evaluation of real patients from a large data set of patients in the Eurofever Registry.

METHODS

A multistep process using consensus formation techniques (Delphi and nominal group technique (NGT)) and statistical evaluations on real patients was used to develop and test the classification criteria[17] (online supplementary figure 1 and supplementary material), based on a methodological framework used successfully in previous studies in rheumatology.[20–25]

Step 1: selection of clinical, laboratory and genetic candidate variables

A panel of 162 international adult and paediatric experienced clinicians completed successive Delphi questionnaires in order to propose and then select and rank the variables (clinical manifestations, genetic analyses, laboratory examinations) from 1 (less important) to 10 (most important), for classification of each HRF[26] and PFAPA.[27]

Step 2: classification of patients from the Eurofever Registry

After selection (online supplementary figure 2), a random sample of 360 patients, 60 patients for each disease (FMF, TRAPS, MKD, CAPS, PFAPA and undefined recurrent fevers (uRF)) were selected from the Eurofever Registry.[28] The inclusion criteria for the enrolment in the registry have been previously described[28] (see online supplementary material).

Twenty-five international experienced clinicians/researchers and eight geneticists (total of 33 panellists) in the field of SAID blinded on patients' original diagnosis were invited to participate in a multiround, secured web process to classify each of the 360 patients into one of six mutually exclusive diagnoses.[29] Clinicians and geneticists worked separately in the first steps (clinicians blinded to genetic results and geneticists blinded to clinical data) and then together to reach consensus ≥80% on all classifiable patients.

Step 3: statistical analysis for the selection of the best candidate classification criteria

The statistical analysis plan (full details in the online supplementary material) foresaw the following steps:

- Evaluation through a univariate logistic regression of the relationship between each individual top variable identified in step 1 and each disease as derived from the panel's classification.
- Computer generation of more than 30 000 new candidate sets of classification criteria through linear combinations of genetic and clinical variables with improper linear modelling. Additionally, 11 sets of criteria were derived from the literature[9–16] or proposed by members of the panel based on their expertise.
- Identification of the top-performing criteria through ranking according to the Akaike information criterion (AIC), with best model having the lowest AIC.

Step 4: NGT Consensus Conference for the selection of the final classification criteria

The Consensus Conference was held in Genoa, Italy, on 18–21 March 2017. Clinicians and geneticists, who participated in the step 2 web consensus classification exercise, attended a meeting. The overall goal of the meeting was to decide on the final set of criteria, using a combination of statistical and consensus (≥80%) formation techniques with the consensus panel classification as reference standard.

Step 5: cross-sectional validation of the final classification criteria

The performance of the final set of classification criteria to discriminate patients with the different HRF and PFAPA was tested, using the original treating physician patients' diagnosis as reference standard for the cross-sectional validation, postconsensus, in a separate set of 1018 patients selected after random computer generation from the Eurofever Registry, which contains all variables included in the final set of classification criteria.

RESULTS

The demographic, clinical, genetic and laboratory features of the 360 patients randomly selected from the Eurofever Registry are provided in table 1 and online supplementary table 1.

A total of 100 different genotypes were reported in the 360 patients included in the classification process as reported in online supplementary table 2.

Nine patients with CAPS and two with TRAPS had no mutations detected using Sanger sequencing; thus, at the time of enrolment, somatic mosaicism could not be formally excluded in them. Low penetrant or incidental (non-confirmatory) genetic findings were also reported in 7 patients with PFAPA and 14 with uRF (online supplementary table 3).

Classification of patients from the Eurofever Registry

In the first two rounds, evaluation of clinical data by clinicians (blinded to genetic results) resulted in consensus of ≥80% for a total of 216 of 360 (60%) patients (figure 1); consensus was reached in 51 patients with MKD, 43 with TRAPS, 29 with FMF, 29 with CAPS, 26 with PFAPA and 38 with uRF. Similarly evaluation of demographic and genetic data by geneticists (blinded

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Table 1 Demographic features of the 360 patients included in the study

	FMF n=60	CAPS n=60	MKD n=60	TRAPS n=60	PFAPA n=60	uRF n=60
Male	30 (50%)	32 (53%)	26 (43%)	35 (58%)	28 (47%)	28 (47%)
Paediatric/Adults	54/6	33/27	45/15	29/31	59/1	39/21
Age, years, median (range)	10.5 (7.0–15.5)	16.0 (8.9–31.6)	16.2 (9.1–23.0)	21.9 (10.5–41.1)	6.6 (3.8–9.5)	13.5 (8.2–26.4)
Age at disease onset, median (range)	3.4 (1.2–6.4)	3.0 (0.5–11.2)	0.4 (0.2–0.9)	3.4 (0.8–10.6)	1.5 (0.7–3.0)	5.9 (2.0–19.1)
Disease duration, median (range)	5.6 (2.7–10.2)	9.0 (4.6–19.1)	14.2 (7.9–20.8)	13.3 (6.8–23.2)	3.9 (2.3–6.8)	4.8 (3.0–8.2)
Episode duration, median (range)	3.0 (2.0–4.0)	2.0 (0.8–5.0)	5.0 (4.0–7.0)	8.0 (5.0–18.0)	4.0 (3.0–5.0)	4.0 (3.0–7.0)
Number episodes/year, median (range)	12.0 (10.0–20.0)	12.0 (6.0–25.0)	12.0 (10.0–16.0)	6.0 (4.0–12.0)	12.0 (12.0–18.0)	12.0 (5.0–13.0)

CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; MKD, mevalonate kinase deficiency; PFAPA, periodic fever, aphthosis, pharyngitis and adenitis; TRAPS, tumour necrosis factor receptor-associated periodic fever syndrome; uRF, undefined recurrent fevers.

to clinical data) in two separate rounds reached consensus on 319 of 360 (89%) with 278 (77%) patients with 80% consensus after the first round. At the end of the two initial rounds, 128 (36%) patients were concordant between the independent evaluation of both the clinicians and the geneticists. At the end of the fourth round, consensus was achieved in 281 of 360 (78%) as follows: 56 (95%) MKD, 39 (76%) TRAPS, 37 (70%) PFAPA, 36 (71%) FMF, 32 (63%) CAPS and 81 (85%) uRF (figure 1, online supplementary table 4). K (concordance coefficient) agreement between the panel reference standard classification and the original patient diagnosis by the treating physician was 0.99 for MKD, 0.87 for TRAPS, 0.86 for CAPS, 0.84 for FMF and 0.68 for PFAPA.

Statistical analysis for the selection of the best classification criteria

The top variables arising from step 1 (see the Methods section) were included in a univariate logistic regression analysis using the 281 patients for which consensus was achieved by the panel as outcome. Clinical variables positively and negatively associated with each disease are reported in online supplementary table 5 with the related OR and 95% CI. The strategy for the classification of the genotypes is described in online supplementary table 6.

A total of 198 over >30 000 possible new sets of classification criteria (available on request; 50 for CAPS, 45 for FMF, 44 for TRAPS, 32 for MKD and 22 for PFAPA) were retained, based on

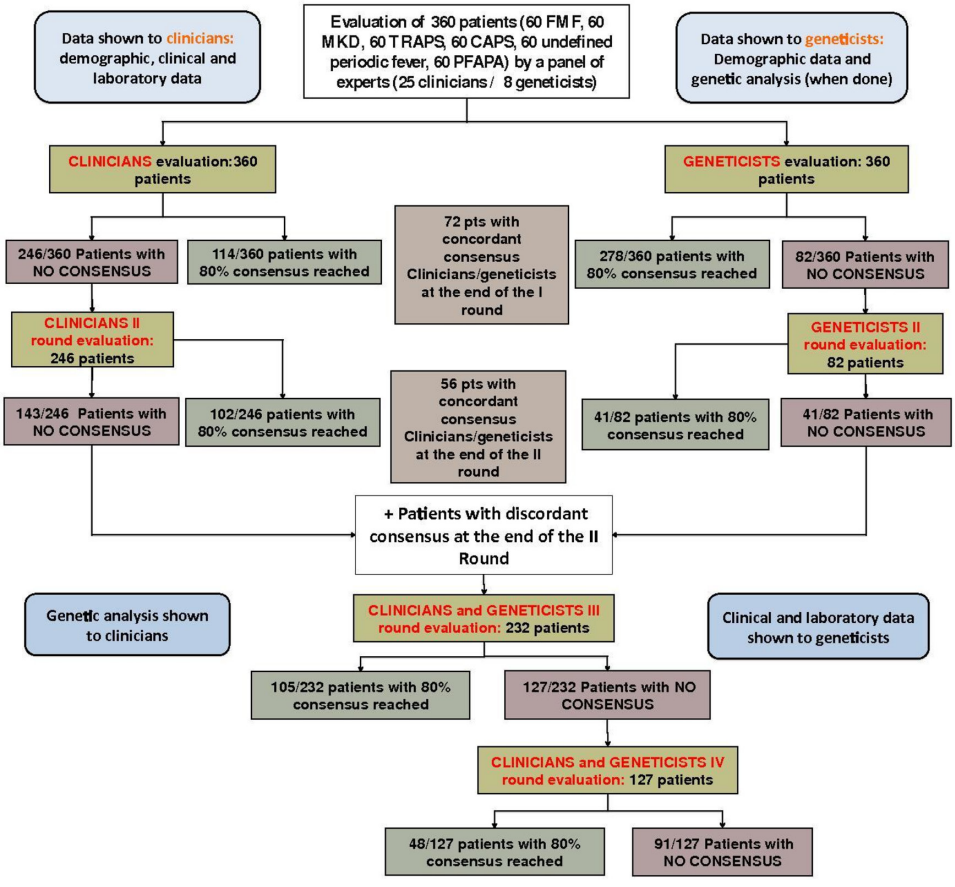
Data shown to clinicians: demographic, clinical and laboratory data
Evaluation of 360 patients (60 FMF, 60 MKD, 60 TRAPS, 60 CAPS, 60 undefined periodic fever, 60 PFAPA) by a panel of experts (25 clinicians / 8 geneticists)
Data shown to geneticists: Demographic data and genetic analysis (when done)
CLINICIANS evaluation:360 patients
GENETICISTS evaluation: 360 patients
246/360 Patients with NO CONSENSUS
114/360 patients with 80% consensus reached
72 pts with concordant consensus Clinicians/geneticists at the end of the I round
278/360 patients with 80% consensus reached
82/360 Patients with NO CONSENSUS
CLINICIANS II round evaluation: 246 patients
GENETICISTS II round evaluation: 82 patients
143/246 Patients with NO CONSENSUS
102/246 patients with 80% consensus reached
56 pts with concordant consensus Clinicians/geneticists at the end of the II round
41/82 patients with 80% consensus reached
41/82 Patients with NO CONSENSUS
+ Patients with discordant consensus at the end of the II Round
Genetic analysis shown to clinicians
CLINICIANS and GENETICISTS III round evaluation: 232 patients
Clinical and laboratory data shown to geneticists
105/232 patients with 80% consensus reached
127/232 Patients with NO CONSENSUS
CLINICIANS and GENETICISTS IV round evaluation: 127 patients
48/127 patients with 80% consensus reached
91/127 Patients with NO CONSENSUS

Figure 1 Flow chart of the consensus nominal group technique for classification of patients from the Eurofever Registry. CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; MKD, mevalonate kinase deficiency; PFAPA, periodic fever, aphthosis, pharyngitis and adenitis; pts, patients; TRAPS, tumour necrosis factor receptor-associated periodic fever syndrome.

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Table 2 New Eurofever/PRINTO classification criteria for hereditary recurrent fevers and their performance in the 281 patients with consensus

CAPS	FMF	TRAPS	MKD
Presence of a *confirmatory NLRP3 genotype** and *at least one* among the following: ► Urticarial rash. ► Red eye (conjunctivitis, episcleritis, uveitis). ► Neurosensorial hearing loss. OR Presence of *not confirmatory NLRP3 genotype*† and *at least two* among the following: ► Urticarial rash. ► Red eye (conjunctivitis, episcleritis, uveitis). ► Neurosensorial hearing loss.	Presence of *confirmatory MEFV genotype** and *at least* one among the following: ► Duration of episodes 1–3 days. ► Arthritis. ► Chest pain. ► Abdominal pain. OR Presence of *not confirmatory MEFV* genotype‡ and *at least two* among the following: ► Duration of episodes 1–3 days. ► Arthritis. ► Chest pain. ► Abdominal pain.	Presence of confirmatory *TNFRSF1A* genotype* and at least one among the following: ► Duration of episodes ≥7 days. ► Myalgia. ► Migratory rash. ► Periorbital oedema. ► Relatives affected. OR Presence of a not confirmatory *TNFRSF1A* genotype† and *at least two* among the following: ► Duration of episodes ≥7 days. ► Myalgia. ► Migratory rash. ► Periorbital oedema. ► Relatives affected.	Presence of a *confirmatory MVK genotype** and *at least one* among the following: ► Gastrointestinal symptoms. ► Cervical lymphadenitis. ► Aphthous stomatitis.
Sensitivity: 1	Sensitivity: 0.94	Sensitivity: 0.95	Sensitivity: 0.98
Specificity: 1	Specificity: 0.95	Specificity: 0.99	Specificity: 1
Accuracy: 1	Accuracy: 0.98	Accuracy: 0.99	Accuracy: 1

A patient with (1) evidence of elevation of acute phase reactants (ESR or CRP or SAA) in correspondence to the clinical flares and (2) careful consideration of possible confounding diseases (neoplasms, infections, autoimmune conditions, other inborn errors of immunity) and a reasonable period of recurrent disease activity (at least 6 months) is classified as having hereditary recurrent fever if the criteria are met.
*Pathogenic or likely pathogenic variants (heterozygous in AD diseases, homozygous or in trans (or biallelic) compound heterozygous in AR diseases).
†Variant of uncertain significance (VUS). Benign and likely benign variants should be excluded.
‡In trans compound heterozygous for one pathogenic *MEFV* variants and one VUS, or biallelic VUS, or heterozygous for one pathogenic *MEFV* variant. See online supplementary table 7 for glossary.
AD, autosomal dominant; AR, autosomal recessive; CAPS, cryopyrin-associated periodic syndromes; CRP, C-reactive protein; ESR, erythocytes sedimentation rate; FMF, familial Mediterranean fever; MKD, mevalonate kinase deficiency; *MVK*, mevalonate kinase; PRINTO, pediatric rheumatology international trial organization; SAA, serum amyloid A; TRAPS, tumour necrosis factor receptor-associated periodic fever syndrome.

their AIC, for further evaluation at the Consensus Conference, together with 11 criteria from the literature (online supplementary figure 4).

NGT Consensus Conference for the selection of the final classification criteria

The performances of all the criteria chosen by the consensus in the 281 patients who reached a consensus are reported in tables 2 and 3 (see also glossary in online supplementary table 7).

The first disease discussed was FMF. After multiple voting sessions, all three tables of experts, which worked independently from each other, showed a complete convergent validity selecting the same top definition number 38 (online supplementary figure 4, session A), including genetic and clinical variables with a positive association (table 2). After general discussion, a second set of criteria based solely on clinical criteria was selected to be used as a possible tool for the indication for molecular analysis or as classification criteria in case genetic testing is not locally available

Table 3 Eurofever/PRINTO clinical classification criteria for PFAPA and hereditary recurrent fevers and their performance in the 281 for whom consensus was achieved

PFAPA	CAPS	FMF	TRAPS	MKD
At least *seven out of* eight: Presence ► Pharyngotonsillitis. ► Duration of episodes, 3–6 days. ► Cervical lymphadenitis. ► Periodicity. Absence ► Diarrhoea. ► Chest pain. ► Skin rash. ► Arthritis.	Presence of *at least two of five**: ► Urticarial rash. ► Cold/Stress-triggered episodes. ► Sensorineural hearing loss. ► Chronic aseptic meningitis. ► Skeletal abnormalities (epiphysial overgrowth/frontal bossing).	At least *six out of nine*: Presence ► Eastern Mediterranean ethnicity. ► Duration of episodes, 1–3 days. ► Chest pain. ► Abdominal pain. ► Arthritis. Absence ► Aphthous stomatitis. ► Urticarial rash. ► Maculopapular rash. ► Painful lymph nodes.	Score ≥5 points: Presence ► Fever ≥7 days (2 points). ► Fever 5–6 days (1 point). ► Migratory rash (1 point). ► Periorbital oedema (1 point). ► Myalgia (1 point). ► Positive family history (1 point). Absence ► Aphthous stomatitis (1 point). ► Pharyngotonsillitis (1 point).	Presence of *at least three of six*: ► Age at onset <1 years. ► Gastrointestinal symptoms. ► Painful lymph nodes. ► Aphthous stomatitis. ► Triggers. ► Maculopapular rash.
Sensitivity: 0.97	Sensitivity: 0.80	Sensitivity: 0.91	Sensitivity: 0.87	Sensitivity: 0.91
Specificity: 0.93	Specificity: 0.91	Specificity: 0.92	Specificity: 0.92	Specificity: 0.82
Accuracy: 0.99	Accuracy: 0.85	Accuracy: 0.97	Accuracy: 0.96	Accuracy: 0.92

*Modified by Kuemmerle-Deschner *et al*.[14] See online supplementary table 6 for glossary. See table 2 for prerequisite criteria.
CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; MKD, mevalonate kinase deficiency; PFAPA, periodic fever, aphthosis, pharyngitis and adenitis; PRINTO, pediatric rheumatology international trial organization; TRAPS, tumour necrosis factor receptor-associated periodic fever syndrome.

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(online supplementary figure 4, session B). To this aim, definition number 12, including clinical variables with both positive and negative association with the disease, was chosen (table 3).

The same approach was followed for the other HRFs (CAPS, TRAPS, MKD), leading to the selection of criteria with genetic and clinical variables (number 32 for CAPS, number 46 for TRAPS, number 37 for MKD) (table 2, online supplementary figures 6-8). As per the process to establish FMF criteria, a set of purely clinical criteria (ie, without genetic results) was also selected for each HRF, namely definitions number 20 and number 1 for MKD and TRAPS, respectively (table 3). For CAPS classification, the experts reached consensus on a modified version of recently published criteria.[14] The performance of the original Kummerle criteria (using two out of six criteria) in the context of the present study population displayed a good sensitivity (0.91), but a low specificity (0.80).[14] In contrast, when the variable 'musculoskeletal pain' was excluded, a higher specificity (0.94, with a sensitivity of 0.80) was achieved, if two out of five criteria are present (table 3). The most severe form of CAPS, chonic infantile neurological cutaneous articular (CINCA)/neonatal onset multisystemic inflammatory disorder (NOMID), displays a chronic rather than a recurrent disease course. Patients with CINCA were not included in the validation process described above. However, when the new genetic and clinical CAPS criteria were tested in a separate set of 70 patients with CAPS with chronic disease course enrolled in the Eurofever Registry, the sensitivity was 100% for the genetic and clinical criteria and 80% for the clinical criteria (not shown).

Clinical classification criteria for PFAPA were discussed between the 25 clinical panellists distributed in two tables (no geneticists). After discussion (online supplementary figure 8), definition number 13 (clinical variables with both positive and negative association) was chosen (table 3). During the Consensus Conference, the panel agreed on a few suggested mandatory criteria that should be fulfilled in all the patients before the application of the new classification criteria (table 3) with a consensus of 100% for point 1 and 96% for point 2.

Globally, convergent validity among the three tables of experts was obtained for the genetic and clinical definitions of FMF and CAPS, whereas for all the other definitions a partial convergent validity (agreement in two out of three tables) was reached, with the need for a final plenary voting session (online supplementary figures 4-8 and online supplementary table 8).

Cross-validation of the final classification criteria

The ability of the new classification criteria to discriminate among the different recurrent fevers and uFR was further tested in the validation data set of 1018 patients extracted from the Eurofever Registry (online supplementary table 9) using as reference standard for each patient the diagnosis given by the treating physician. In the last column of table 4, the genotype (score 0=negative/not done; score 1=not confirmatory; score 2=confirmatory) of patients not identified by the clinical criteria for HRF is reported. Notably, almost all the patients not classified by the clinical and genetic criteria displayed a negative or not confirmatory genotype (table 4). The performance of the new classification criteria (either clinical and genetic or clinical only) was generally superior (accuracy ranging from 0.81 to 0.98; table 4) to those already available in the literature (accuracy 0.56–0.94) (online supplementary table 10).

DISCUSSION

The present study provides new evidence-based classification criteria for the four 'classical' HRF (FMF, MKD, TRAPS, CAPS) and PFAPA, incorporating combined consensus expertise of clinicians and geneticists with statistical analyses in real patients from the Eurofever Registry. At variance with past work[15] these new classification criteria combine genetic and clinical variables to overcome the paradox of the absence of a role of the molecular analysis for the proper identification of patients affected by these (mainly) genetic conditions. As defined by the American College of Rheumatology, the proposed classification criteria have selected clinical and genetic findings able to identify the defined diseases and separate from other confounding autoinflammatory conditions.[18 19] Although these criteria may at times be helpful in clinical practice, they are explicitly not meant to be employed as diagnostic criteria. The advent of the so-called next-generation sequencing era resulted on one side to an increased availability of the molecular analysis at reduced costs but might often lead to difficulties in the proper interpretation of this large set of bioinformatic data. In fact, besides the identification of clearly pathogenic variants, in many circumstances (ie, low penetrance variants or variants of unknown significance, monoallelic variants in autosomal recessive diseases, presence of variants in more than one gene) the genetic results are not unequivocal and should be placed in the context of a pertinent clinical setting. In these latter cases, the classification of the patient is usually problematic, as clearly shown in the process of patients' validation in this study. For these reasons, the panel decided to introduce a distinction between a confirmatory (namely, surely or likely pathogenic variants) and not confirmatory (variants of unknown significance) genetic test. For the daily use of the new criteria, a parallel consensus classification effort by the genetic subcommittee of the INSAID project has established the pathogenicity of each currently known variant associated to HRF.[30] A differential approach for the interpretation of the biallelic variants was chosen for the two autosomal recessive diseases, namely MKD and FMF. MKD is caused by loss-of-function mutations in the *MVK* gene. The panel excluded the possibility of classifying a patient as an MKD in the absence of biallelic mutations of the *MVK* gene. Conversely, recent evidence has clarified that FMF is secondary to gain-of-function mutations of the *MEFV* gene, with a clear dose effect,[31 32] and therefore FMF could be classified with identification of either one or two pathogenic variants in exon 10 of *MEFV* in the presence of a consistent clinical phenotype. The same possibility was also considered for the two autosomal dominant diseases, CAPS and TRAPS, in the absence of confirmatory phenotype. In patients carrying variants of unknown pathogenic significance (such as R92Q and P46L for *TNFRSF1A*, or V198M for *NLRP3*),[33–36] only the presence of some very specific clinical variables would support the proper disease classification. In parallel with the elaboration of the definitive criteria that include genetic/clinical variables, the panel agreed on additional clinical criteria that should be used to (1) identify patients with recurrent fevers that would need to undergo genetic testing for molecular confirmation; (2) search for possible somatic mosaicism using NG in patients with a clear phenotype, but negative Sanger sequencing results; and (3) classify patients (eg, for epidemiological studies) even in those countries where routine genetic testing is not possible. For PFAPA, the contemporary evaluation of either positive (presence) and negative (absence) clinical variables yielded a much higher accuracy when compared with the classical modified Marshall's criteria.[16] Following the consensus meeting, the new sets of criteria were

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Table 4 Performance of the new classification criteria to discriminate different recurrent fevers in the validation data set of patients extracted from the Eurofever Registry (N=1018)

	Positive/Negative	OR	Sensitivity	Specificity	Accuracy	AUC	Patients not fulfilling the criteria	Number of patients not fulfilling the clinical criteria but satisfying the clinical/genetic criteria
CAPS clinical + genetics	TP: 98/1013 TN: 877/1013 FP: 0/1013 FN: 38/1013	4490	0.72	1	0.96	0.86	27/38 pts, score 0 (71.05%) 10/38 pts, score 1 (26.32%) 1/38 pts, score 2 (2.63%)	
CAPS clinical	TP: 82/925 TN: 806/925 FP: 12/925 FN: 25/925	220.3	0.77	0.99	0.96	0.88	3/25 pts, score 0 (13.04%) 8/25 pts, score 1 (34.78%) 12/25 pts, score 2 (52.17 %)	Score 0: 0/3 Score 1: 1/8 Score 2: 11/12
FMF clinical + genetics	TP: 304/1010 TN: 664/1010 FP: 3/1010 FN: 39/1010	1725.3	0.89	1	0.96	0.94	12/39 pts, score 0 (30.77%) 26/39 pts, score 1 (66.67%) 1/39 pts, score 2 (2.56%)	
FMF clinical	TP: 283/940 TN: 568/940 FP: 39/940 FN: 50/940	82.4	0.85	0.94	0.91	0.89	3/50 pts, score 0 (6,12%) 26/50 pts, score 1 (53,06%) 20/50 pts, score 2 (40,82 %)	Score 0: 0/3 Score 1: 8/26 Score 2: 19/20
MKD clinical + genetics	TP: 45/1005 TN: 944/1005 FP: 0/1005 FN: 16/1005	5209.1	0.74	1	0.98	0.87	2/16 pts, score 0 (12.5%) 14/16 pts, score 1 (87.5%)	
MKD clinical	TP: 43/818 TN: 617/818 FP: 144/818 FN: 14/818	13.2	0.75	0.81	0.81	0.78	2/14 pts, score 1 (15.38%) 11/14 pts, score 2 (84.62%)	Score 1: 0/2 Score 2: 10/11
TRAPS clinical + genetics	TP: 73/1000 TN: 900/1000 FP: 1/1000 FN: 26/1000	2526.9	0.74	1	0.97	0.87	6/26 pts, score 0 (23.08%) 20/26 pts, score 1 (76.92%)	
TRAPS clinical	TP: 52/940 TN: 813/940 FP: 33/940 FN: 42/940	30.4	0.55	0.96	0.92	0.76	27/42 pts, score 1 (71.05%) 11/42 pts, score 2 (28.95 %)	Score 1: 8/27 Score 2: 11/11
PFAPA clinical	TP: 149/1001 TN: 752/1001 FP: 24/1001	61.4	0.66	0.97	0.9	0.82		

For explanation of the scores 0–1–2, see online supplementary table 6.
CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; FN, false negative; FP, false positive; MKD, mevalonate kinase deficiency; PFAPA, periodic fever, aphthosis, pharyngitis and adenitis; pts, patients.TN, true negative; TP, true positive; TRAPS, tumour necrosis factor receptor-associated periodic fever syndrome;

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further validated in a large group of additional patients from the Eurofever Registry, showing a very high specificity when compared with previous literature criteria. As noticed, most of the diagnoses refuted by the new criteria had been in patients with either non-confirmatory or negative genetic tests results. It is therefore conceivable that the present new criteria will be more stringent in the classification of patients, by excluding a substantial proportion of patients carrying variants of unknown origin. The classification criteria we propose are accurate for the discrimination of one form of autoinflammation from another in the context of the six conditions considered herein, but very much have to be applied judiciously, after careful consideration of confounding diseases, as highlighted in table 2. These classification criteria are therefore intended for use for clinical, epidemiological or translational studies, but not for routine diagnostic purposes in individual patients.[37] That said, the purely clinical classification criteria might guide molecular testing approaches for individual cases, although this point requires future validation. One possible limitation of the present study is the lack of comparison groups including possible confounding conditions (chronic infections, neoplasms, immune deficiencies, autoimmune disease and metabolic diseases) presenting sometimes with a recurrent disease course. In daily practice confounding diseases with a true recurrent disease course are rather infrequent outside HRF and PFAPA, while the most challenging group of confounding conditions are the large emerging group of patients with uRF, many of whom may have a true monogenetic cause other than the four genetic diseases considered herein. For these reasons, the different HRFs have been used as controls for each individual condition with PFAPA and uRF as genetically negative controls. The panel of experts unanimously decided that the presence of elevation of acute phase reactants during disease flares (recorded at least in one occasion) should be considered as *mandatory* preliminary criterion for the use of the new classification criteria.[14] Some other relevant pathognomonic laboratory examinations, such as urinary mevalonic acid in MKD, were not available in the Eurofever Registry, probably reflecting the fact that it is not widely available for testing routinely. As such the panel recommended the importance for the diagnostic work-up, for example, with intracellular MVK enzyme activity and/or urinary mevalonic acid in MKD,[38] particularly for patients with convincing phenotypes but non-confirmatory genotype for MKD. Similarly, the response to some specific treatments (such as colchicine in FMF or anti-interleukin (IL)-1 in CAPS) or ethnic background (for FMF) could certainly be considered as additional elements to be considered in daily practice, especially for patients with non-confirmatory genotype, but are not good discriminators of the different forms of autoinflammatory disease considered herein. In conclusion, the present work allowed the proposal of novel evidence-based classification criteria for HRF and PFAPA with a high specificity. The use of these classification criteria is highly recommended for inclusion of patients in translational and clinical studies, including clinical trials, and should not be misused as diagnostic criteria.[17] The possible identification of new genetic entities in the heterogeneous group of undefined periodic fevers could require an update of the criteria in the future.

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EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies

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ABSTRACT

The therapeutic management of Sjögren syndrome (SjS) has not changed substantially in recent decades: treatment decisions remain challenging in clinical practice, without a specific therapeutic target beyond the relief of symptoms as the most important goal. In view of this scenario, the European League Against Rheumatism (EULAR) promoted and supported an international collaborative study (EULAR SS Task Force) aimed at developing the first EULAR evidence and consensus-based recommendations for the management of patients with SjS with topical and systemic medications. The aim was to develop a rational therapeutic approach to SjS patients useful for healthcare professionals, physicians undergoing specialist training, medical students, the pharmaceutical industry and drug regulatory organisations following the 2014 EULAR standardised operating procedures. The Task Force (TF) included specialists in rheumatology, internal medicine, oral health, ophthalmology, gynaecology, dermatology and epidemiology, statisticians, general practitioners, nurses and patient representatives from 30 countries of the 5 continents. Evidence was collected from studies including primary SjS patients fulfilling the 2002/2016 criteria; when no evidence was available, evidence from studies including associated SjS or patients fulfilling previous sets of criteria was considered and extrapolated. The TF endorsed the presentation of general principles for the management of patients with SjS as three overarching, general consensus-based recommendations and 12 specific recommendations that form a logical sequence, starting with the management of the central triplet of symptoms (dryness, fatigue and pain) followed by the management of systemic disease. The recommendations address the use of topical oral (saliva substitutes) and ocular (artificial tear drops, topical non-steroidal anti-inflammatory drugs, topical corticosteroids, topical CyA, serum tear drops) therapies, oral muscarinic agonists (pilocarpine, cevimeline), hydroxychloroquine, oral glucocorticoids, synthetic immunosuppressive agents (cyclophosphamide, azathioprine, methotrexate, leflunomide and mycophenolate), and biological therapies (rituximab, abatacept and belimumab). For each recommendation, levels of evidence (mostly modest) and TF agreement (mostly very high) are provided. The 2019 EULAR recommendations are based on the evidence collected in the last 16 years in the management of primary 2002 SjS patients and on discussions between a large and broadly international TF. The recommendations synthesise current thinking on SjS treatment in a set of overarching principles and recommendations. We hope that the current recommendations will be broadly applied in clinical practice and/or serve as a template for national societies to develop local recommendations.

INTRODUCTION

Sjögren syndrome (SjS), a systemic autoimmune disease that affects 1–23 persons per 10 000 inhabitants in European countries,[1] presents with a wide spectrum of clinical manifestations and autoantibodies. Antinuclear antibodies are the most frequently detected autoantibodies, anti-Ro/SS-A the most specific, and cryoglobulins and hypocomplementaemia the main prognostic markers.[2] The histological hallmark is a focal infiltration of the exocrine glands by lymphocytes, determined by minor labial salivary gland biopsy. The clinical scenario is dominated by sicca syndrome caused by immune-mediated glandular involvement, accompanied by fatigue, musculoskeletal pain and systemic features in a significant percentage of patients, and complicated by lymphoma in around 2%–5% of patients.[3] When SjS appears in a previously healthy person, the disease is classified as primary, while patients with concomitant systemic autoimmune diseases (SAD) are classified as associated (or secondary) SjS; since this distinction only reflects a clinical situation of autoimmune coexistence the term SjS will be throughout the manuscript. SjS patients make substantial use of healthcare services, with a mean annual total direct cost per patient ranging between £2200 in UK and US$20 000 in the USA.[4 5]

The therapeutic management of SjS has not changed substantially in recent decades[6] and is still based on symptomatic treatment of sicca

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symptomatology and broad-spectrum immunosuppression for systemic disease, with insufficient information on the differential efficacy and safety of the therapeutic options available.[7] Treatment decisions remain challenging in clinical practice, without a specific therapeutic target beyond the relief of symptoms as the most important goal. Therefore there is growing interest in the proposal of clinical guidelines by national scientific societies.[8–11]

In 2010, the European League Against Rheumatism (EULAR) promoted and supported an international collaborative study (EULAR SS Task Force) aimed at developing disease-specific activity indexes in SjS (EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and EULAR Sjögren's syndrome disease activity index (ESSDAI) scores),[12 13] which are now widely used both clinically and in research. A second project, the development of the first EULAR evidence and consensus-based recommendations for the management of patients with SjS with topical and systemic medications, was proposed and launched.

METHODS

After approval of the proposal by the EULAR Executive Committee, the convenor (MR-C) and co-convenors (CV, SB, XM) invited international experts with a solid history of clinical research in SjS (most of whom were previously involved in the ESSDAI/ESSPRI project) to form part of a Steering Committee (SC) and a Task Force (TF), which also included methodologists, patient representatives and individuals from all relevant professional groups (online supplementary appendix 1). The aim was to develop a rational therapeutic approach to SjS patients that would be useful for healthcare professionals, doctors in specialist training, medical students, the pharmaceutical industry and drug regulatory organisations following the 2014 EULAR standardised operating procedures.[14] Industry involvement was not permitted at any stage of the project.

Steering committee

The SC included 13 rheumatologists, four internal medicine, one primary care and one oral health specialists, one epidemiologist, one statistician, one healthcare professional representative and two patient representatives. The SC agreed on some principal considerations upfront: (a) The statements were termed 'recommendations' as opposed to 'guidelines' or 'points to consider' because they offer guidance, which needs to be tailored to meet individual requirements. (b) Some general rules and definitions (overarching principles, general recommendations, definition of sequential therapeutic schedules, severity or refractoriness) cannot be evidence-based and were, therefore based on consensus. (c) The remaining statements were evidence-based, that is, supported by the highest level of evidence possible, limiting statements based only on retrospective data (although for some clinical or therapeutic scenarios with no data in controlled studies, this was allowed if the amount of retrospective data was considered significant and scientifically reliable); recommendations based on data obtained from case reports were not allowed. (d) Evidence was collected from studies including primary SjS patients fulfilling the 2002/2016 criteria (SjS-2002).[15 16] When no evidence was available, evidence from studies including associated SjS, patients fulfilling previous sets of criteria or those including a mix of autoimmune and non-autoimmune aetiologies was considered and extrapolated (online supplementary table S1). (e) The balance between efficacy and side effects was evaluated agent by agent. (f) Although recommendations are primarily supported by the evidence reported in patients with primary SjS, the advice on topical and systemic management contained in these guidelines may be applicable to patients with associated (or secondary) SjS.

Systematic literature review

A previous systematic literature review (SLR) reported by the convenor in 2010[7] served to provide SC members with a background to initiate discussions and propose research questions for the SLR focused on the therapeutic management of SjS. On the basis of the research questions, PBZ and SR carried out the SLR between January 1986 and December 2017, with the supervision of the convenor and the methodologists. Summary-of-findings (SoF) tables were generated and levels of evidence (LoE) were determined according to the study design, using the Oxford CEBM standards[17] (online supplementary table S1). The SoFs of the SLR were presented to the SC, whose members formulated a first draft of recommendations based on this information, using electronic and cloud-based working strategies to review the literature search, making comments and maintaining open communication for electronic discussion and amendments. The SLR informing the SC and TF and a detailed description of the methods is published separately. [18] (

Task Force

The TF (online supplementary appendix 1) included 77 specialists in rheumatology, internal medicine, oral health, ophthalmology, gynaecology, dermatology and epidemiology, statisticians, general practitioners, nurses and patient representatives from 30 countries of the five continents (Argentina, Australia, Brazil, Canada, China, Denmark, Egypt, Finland, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Norway, Poland, Portugal, Slovenia, South Korea, Spain, Sweden, Switzerland, the Netherlands, Turkey, the UK and the USA). All TF members declared all potential conflicts of interest. After presentation of the SLR results and the SC proposals to the TF in the first face-to-face meeting, the TF was split into nine breakout working groups (see online supplementary text). Each group proposed draft language and diagnostic/therapeutic algorithms for the respective recommendations to the whole TF. Safety aspects were addressed in each breakout group. Formal economic analyses were not performed, but cost aspects were considered throughout the process. Representatives of each breakout group reported the results of the respective deliberations and presented proposals for the wording of individual recommendations to the whole TF for further discussion and refinement in the second face-to-face meeting.

Consensus findings

After the second meeting, a web-based Delphi procedure was carried out using online voting.[19] The Delphi procedure was designed by MR-C and PB-Z, and developed, managed and analysed by BK using Google Forms; all clinical experts in SjS included in the TF were invited to participate in the Delphi procedure. For an overarching principle or recommendation to be accepted for the final document, TF members were asked to grade for priority according to the level of importance in the daily therapeutic management of SjS (from 1 as unimportant, no priority, no relevance to 5 as very important, a most relevant point, first-order priority); a specific section allowed the inclusion of comments suggested to accompany individual items. Recommendations scoring ≥4 ('important') by >80% of participants were accepted; if this result was not achieved, the respective text was amended and subjected to a second electronic ballot. The approved recommendations were subjected to

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Table 1 Overarching (A–C) and specific (1–12) recommendations

	LoE	GoR	Vote (%)	LoA (0–10)
A.Patients with SjS should be managed at, or in close collaboration with, centres of expertise following a multidisciplinary approach	NA	NA	90	9.2
B.The first therapeutic approach for dryness should be symptomatic relief using topical therapies	NA	NA	93	8.9
C.Systemic therapies may be considered for the treatment of active systemic disease	NA	NA	90	9.1
1.Baseline evaluation of salivary gland function is recommended before starting treatment for oral dryness	5	D	81	8.7
2.The preferred first therapeutic approach for oral dryness according to salivary gland function may be:	1a/*1b	B	88	8.7
2.1. Non-pharmacological stimulation for mild dysfunction;				
2.2. Pharmacological stimulation* for moderate dysfunction;				
2.3. Saliva substitution for severe dysfunction				
3.The first-line therapeutic approach to ocular dryness includes the use of artificial tears and ocular gels/ointments	1a	B	98	9.5
4.Refractory/severe ocular dryness may be managed using topical immunosuppressive-containing drops* and autologous serum eye drops	1a/*1b	B/D	94	9.1
5.Concomitant diseases should be evaluated in patients presenting with fatigue/pain, whose severity should be scored using specific tools	5	D	93	9.0
6.Consider analgesics or other pain-modifying agents for musculoskeletal pain, considering the balance between potential benefits and side-effects	4	C	89	8.9
7.Treatment of systemic disease should be tailored to organ-specific severity using the ESSDAI definitions	4	C	89	9.0
8.Glucocorticoids should be used at the minimum dose and length of time necessary to control active systemic disease	4	C	85	9.6
9.Immunosuppressive agents should be mainly used as GC-sparing agents, with no evidence supporting the choice of one agent over another	4	C	82	8.9
10.B-cell targeted therapies may be considered in patients with severe, refractory systemic disease	1b	B	98	8.6
11.The systemic organ-specific therapeutic approach may follow, as a general rule, the sequential (or combined) use of GCs, immunosuppressive agents and biologics	5	D	98	8.6
12.Treatment of B-cell lymphoma should be individualised according to the specific histological subtype and disease stage	4	C	88	9.7

LoE and GoR according to the Oxford Centre for Evidence-based Medicine—LoE (March 2009). Vote (%): % of participants scoring the recommendation as at least 'important' (score of ≥4 on 5-point scale). LoA: mean score (scale of '0' as no agreement, '10' full agreement).
ESSDAI, EULAR Sjögren's syndrome disease activity index; EULAR, European League Against Rheumatism; GC, glucocorticoid; GoR, grade of recommendation; LoA, levels of agreement; LoE, levels of evidence; NA, not applicable.

an anonymous electronic vote on the levels of agreement (LoA). Each recommendation was adjudicated on a scale of 0–10 (0, no agreement; 10, full agreement).

The draft of the manuscript was written by MR-C and PB-Z and was sent to TF members for comment and, after incorporating these comments, to the EULAR Executive Committee for review and approval. Final remarks were obtained from members of the TF and the Executive Committee and addressed in the manuscript (all modifications required approval by the SC), which was then submitted with the final approval of the EULAR Executive Committee after being presented in the EULAR 2019 meeting.[20]

RESULTS

General recommendations

As in other EULAR recommendations, the TF endorsed the presentation of general principles for the management of patients with SjS as overarching, general consensus-based recommendations, since the contents were so generic that there was no requirement to base them on the SLR (table 1).

Patients with SjS should be managed at, or in close collaboration with, centres of expertise using a multidisciplinary approach(*LoE na; LoA 9.2*)

SjS may be a serious systemic disease, not only due to the heavy impact on the health-related quality of live (HRQoL) of the predominant symptoms (the triplet of dryness, fatigue and pain), but also due to the involvement of internal organs (systemic involvement) and the excess mortality caused by cancer (lymphoma). The low frequency of SjS in the general population, combined with a heterogeneous glandular/systemic clinical expression, makes it difficult to ensure a standardised depth of expertise in managing the disease in non-specialised clinical settings. Therefore, we recommend organising SjS management in and around centres of expertise, including professionals with solid clinical experience in assessing patients with SAD. Assessment of SjS patients requires expert guidance, not only to confirm the diagnosis by ruling out non-autoimmune aetiologies (especially for sicca symptoms), but also to evaluate the extent of organs damaged and to design a specific personalised follow-up according to the clinical and biological patient phenotype at diagnosis.[21] A multidisciplinary approach involving various health professionals is essential, with a central role for specialists in autoimmune diseases, who should act as the coordinator of diagnostic and therapeutic healthcare processes, based on a shared-decision policy between the patient and the specialist. The involvement of primary care physicians and other health professionals is highly recommended in the management of SjS patients.

The first therapeutic approach to dryness should be symptomatic relief using topical therapies (*LoE na; LoA 8.9*)

More than 95% of SjS patients present with sicca symptoms,[22] which have a significant impact on the HRQoL.[23–25] Studies that have evaluated the natural history of glandular function in primary SjS (summarised by Haldorsen *et al*)[26] report that, except in early stages of the disease, dysfunction may remain stable for long periods of time (up to 12 years) and have a chronic course, and no study has demonstrated that any therapeutic intervention can reverse glandular dysfunction and, therefore, can cure sicca symptoms. Since the complete disappearance of dryness, which is the desired target for all patients,

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Table 2 Glossary and definitions

Term	Definition	Examples
1.Nomenclature of therapies 1.1. Topical therapies 1.2. Systemic therapies	1.1. Interventions directly applied to the mucosal surfaces involved 1.2. Drugs administered orally or intravenously for systemic disease	1.1. Saliva substitutes, ocular tears 1.2. Antimalarials, glucocorticoids, immunosuppressive agents, intravenous immunoglobulins, biologics
2.Disease activity terms 2.1. Systemic disease 2.2. Active systemic disease 2.3. Severe systemic disease 2.4. Refractory systemic disease 2.5. Therapeutic response	2.1. Disease involvement that affects or has affected any of the organs/systems included in the clinESSDAI score 2.2. Patients with clinESSDAI score ≥1. 2.3. Patients with ESSDAI score >14, or high activity in any of the ESSDAI domains with a definition of high activity 2.4. Systemic manifestation/s refractory to SOC. 2.5. Decrease of ≥3 points in the global ESSDAI score	2.1. All ESSDAI domains except biological domain 2.2. Systemic activity is classified as low if ESSDAI is 1–4 (if not only due to biological domain), moderate between 5–13 and high ≥14. 2.3. Lymphadenopathy and lymphoma, articular, cutaneous, pulmonary, renal, muscular central and peripheral neurological and haematological domains. 2.4. Due to the diversity of systemic manifestations, SOC (first-line therapeutic approach) has been defined for each systemic manifestation (figure 3) –
3.Ocular dryness 3.1. Refractory 3.2. Severe	3.1. Refractory ocular dryness is defined as not improvement after using the best-available SOC and ruling out other SjS-unrelated processes, 3.2. Severity should be defined after a specific ophthalmological evaluation of corneal damage by ocular scores:	3.1. SOC defined as the maximum use of artificial tears and ointments according to the previous recommendation 3.2. Measurement of the OSS and OSDI ocular scores
4.Recommended instruments of measure 4.1. Salivary gland function 4.2. Corneal damage 4.3. Fatigue 4.4. Pain 4.5. Quality of life 4.6. Systemic disease	4.1. UWSF, SWSF 4.2. OSS, OSDI 4.3. ESSPRI domains, ProFAD 4.4. ESSPRI domains, BPI 4.5. ESSPRI 4.6. ESSDAI, clinESSDAI	
5.Potential life-threatening systemic manifestations	5.1. Cutaneous domain 5.2. Pulmonary domain 5.3. Renal domain 5.4. Muscular domain 5.5. Peripheral nerve system domain 5.6. CNS domain 5.7. Haematological domain	5.1. Diffuse vasculitis with ulcers 5.2. ILD with NHYA III/IV 5.3. Renal failure; rapidly-progressive glomerulonephritis; hypokalaemic paralysis 5.4. Muscular involvement with severe weakness 5.5. Neuropathy (including ganglionopathy and polyradiculopathies) with severe motor deficit/ataxia; cryoglobulinemic-related multineuritis 5.6. Demyelinating disease with motor deficit; cerebral vasculitis presenting with focal deficit; myelitis; meningoencephalitis 5.7. Severe haemolytic anaemia (<80 g/dL, <50 x109/L); severe autoimmune thrombocytopenia (<50 000/mm3)

BPI, brief pain inventory; CHB, congenital heart block; CIDP, chronic inflammatory demyelinating polyradiculopathy; CNS, central nervous system; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; EULAR, European League Against Rheumatism; G-CSF, granulocyte colony-stimulating factor; ILD, interstitial lung disease; KCS, keratoconjunctivitis sicca; LIP, lymphoid interstitial pneumonitis; MMF, mycophenolate mofetil; MP, methylpredisolone; MS, multiple sclerosis; NAC, N-acetylcysteine; NHYA, New York Heart Association; NMOSD, neuromyelitis optica spectrum disorder; NSIP, non-specific interstitial pneumonitis; OP, organising pneumonitis; OSDI, Ocular Surface Disease Index; OSS, Ocular Staining Score; PN, peripheral neuropathy; ROR, retinoic acid-related orphan receptor; RTX, rituximab; SjS, Sjögren syndrome; SOC, standard of care; STAT, signal transducer and activator of transcriptionm; SWSF, stimulated whole salivary flows; TOR, mammalian target of rapamycin; UIP, usual interstitial pneumonitis; UWSF, unstimulated whole salivary flows.

is at present unreachable, the TF recommends exploring the use of other, more realistic outcomes, such as the minimal clinically-important improvement or the patient-acceptable symptom state, following the corresponding ESSPRI definitions,[13] always closely aligned with patient education, including coping strategies. The chronic course of SjS means a daily, long-term use of therapies and, in this scenario, it is reasonable to recommend the use of therapies with a minimum of (or at least tolerable and reversible) side effects. This is overwhelmingly fulfilled by topical therapies (see definition in table 2). Various studies and Cochrane SLRs support the daily use of topical therapies for the symptomatic relief of dryness, with a significant improvement in HRQoL without significant side effects.[7 27 28] These therapies should be immediately initiated after objective confirmation of glandular dysfunction.

Systemic therapies may be considered for the treatment of active systemic disease (*LoE na; LoA 9.1*)

Systemic disease is a key prognostic determinant of SjS and is linked to autoimmune-mediated organ/s dysfunction that may eventually become irreversible. The use of systemic immunomodulatory/immunosuppressive therapies (glucocorticoids (GCs), antimalarials, immunosuppressive agents, intravenous immunoglobulins and biologics) should be restricted to patients with active systemic disease (see definition in table 2) but only after a careful organ-by-organ evaluation of both severity and organ damage, since not all patients with active systemic disease will necessarily require systemic therapy (this was why the original wording using 'should be' was changed to 'may be'). As a general rule, the management of systemic features in SjS should follow a schedule consisting of a two-stage sequential regimen as used in other SAD, including a first intensive immunosuppressive approach targeted to restore organ function (induction of remission) as soon as possible, followed by a second therapeutic course aimed at maintaining the initial therapeutic response (maintenance of remission). Unfortunately, there are no available data in patients with SjS to support specific recommendations on the need for/duration of induction and maintenance therapies, which should therefore be decided on case-by-case.

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Specific recommendations

The 12 specific recommendations form a logical sequence, starting with the management of the central triplet of symptoms (dryness, fatigue and pain) followed by the management of systemic, extraglandular disease (table 1).

Baseline evaluation of salivary gland function is recommended before starting treatment for oral dryness (*LoE 5, LoA 8.7*)

The therapeutic approach to oral dryness should be driven by the baseline measurement of salivary glandular function, and not by the patient's subjective feelings, since environmental and personal stressing factors may influence the subjective feeling of dryness,[29] which often does not match with the objective measurement of glandular function. We recommend the baseline evaluation of salivary glandular function by measuring whole salivary flows before starting therapeutic interventions, always ruling out SjS-unrelated conditions (ie, candidiasis, burning mouth syndrome); salivary scintigraphy may also be considered.[30] This item elicited significant discussions about the specific tests for measuring glandular function (unstimulated whole salivary flows and stimulated whole salivary flows (SWSF), and salivary scintigraphy), especially the use of SWSF and salivary scintigraphy, which were considered as complicated tests in daily practice by several TF members, and not always available in all clinical settings.

The preferred first therapeutic approach for oral dryness according to salivary gland function may be: Non-pharmacological stimulation for mild dysfunction; pharmacological stimulation for moderate dysfunction*; saliva substitution for severe dysfunction (*LoE 1a/*1b, LoA 8.7*)

On the basis of the results obtained in the measurement of salivary gland function, the therapeutic approach to oral dryness may be initiated based on two mechanisms: salivary gland stimulation (non-pharmacological or pharmacological) or saliva substitution (figure 1).[31]

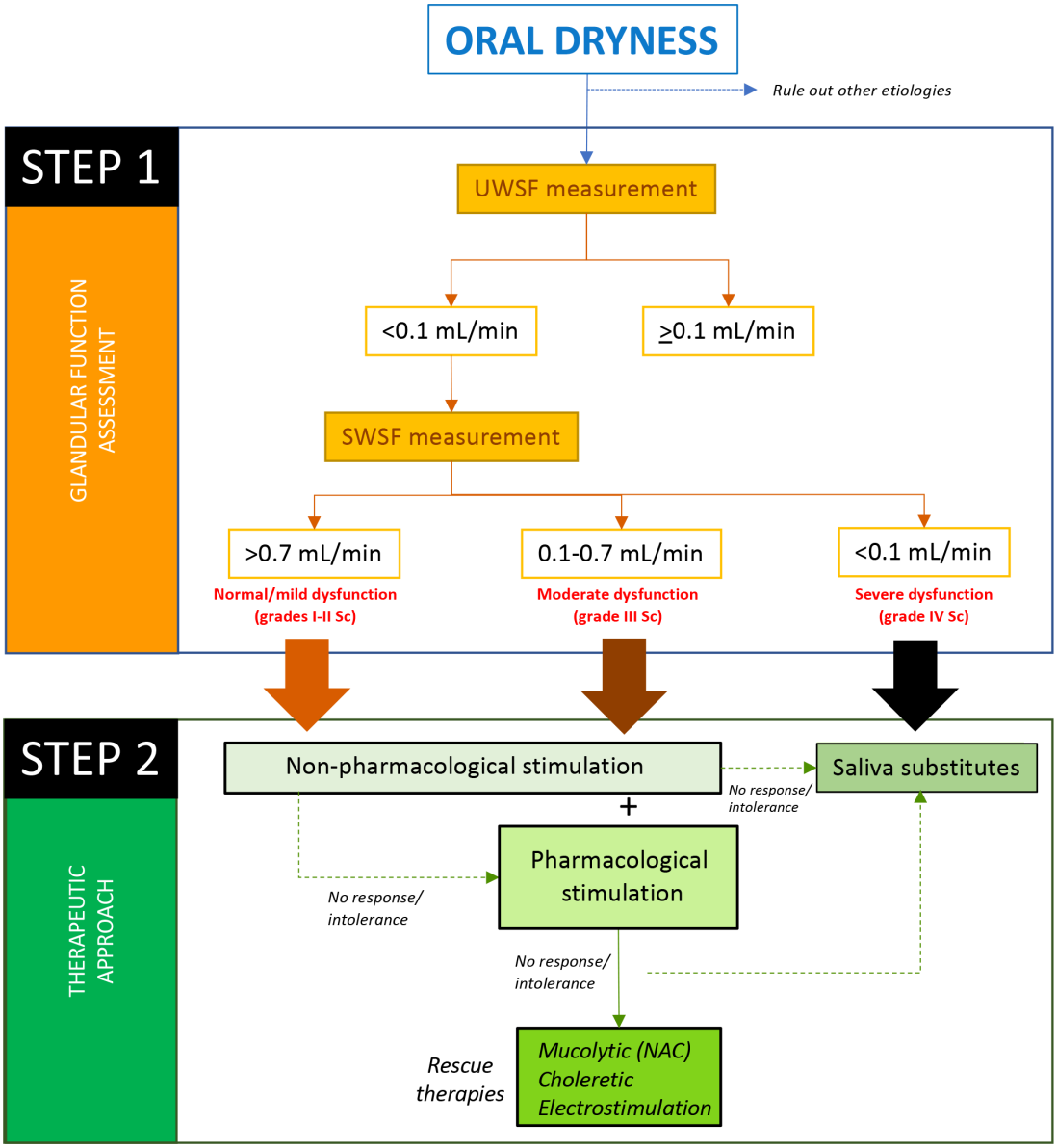

Figure 1 Algorithm of glandular function assessment and therapeutic approach in patients with primary SjS presenting with oral dryness. SjS, Sjögren syndrome; SWSF, stimulated whole salivary flows; UWSF, unstimulated whole salivary flows.

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Non-pharmacological stimulation

In patients with mild glandular dysfunction, we recommend non-pharmacological glandular stimulation as the preferred first-line therapeutic approach, using gustatory stimulants (sugar-free acidic candies, lozenges, xylitol) and/or mechanical stimulants (sugar-free chewing gum) since, in these patients, glandular function can be stimulated (figure 1). With no evidence available for pSjS-2002 patients, evidence was extrapolated from a Cochrane SLR[27] focussed on the therapeutic management of oral dryness; the authors concluded that all non-pharmacological interventions evaluated relieve subjective symptoms to some, unquantified degree, without strong evidence that any intervention was more effective than another, although no study evaluated the therapeutic response according to the degree of salivary gland dysfunction.[27]

Pharmacological stimulation

In patients with moderate glandular dysfunction, pharmacological stimulation with muscarinic agonists may be considered. Two drugs (pilocarpine and cevimeline) are licensed for the treatment of oral dryness, although only pilocarpine is licensed worldwide. The three pivotal randomised controlled trials (RCTs) included both primary and associated SjS patients fulfilling the 1993 criteria, and found significant improvements in visual analogue scale (VAS) dry mouth and salivary flow rates, with a high frequency of adverse events.[7] The available evidence in pSjS-2002 patients is limited to one small prospective study using pilocarpine that found improvement in subjective but not objective oral outcomes,[32] and a second study with no detailed information about overall efficacy and safety.[33] A third retrospective study which compares pilocarpine and cevimeline, only focussed on the safety profile,[34] and reported a better tolerance profile for cevimeline. The evidence is too limited to make a strong recommendation for pSjS-2002 patients (the best level of evidence should be extrapolated from RCTs including patients fulfilling the former 1993 criteria). For this reason, and together with the unfavourable safety profile of these drugs, we recommend offering a trial of muscarinic agonists to patients with moderate glandular dysfunction (or in those with mild dysfunction who are refractory or who do not wish to use non-pharmacological stimulation) (LoE 1b, GoR B) (figure 1). To reduce the main side effect (excess sweating), and based on clinical practice, some TF experts recommended increasing the dose progressively up to 15 to 20 mg/day when possible. In patients who are intolerant or non-responders to muscarinic agents, some choleretic (anetholtrithione) or mucolytic (bromhexine, N-acetylcysteine) agents used as secretagogues in SjS since the 1980s may be considered as rescue therapies due to their good safety profile in the absence of alternative therapeutic options, and taking into account the limitations of the study design and the marginal benefits reported by most studies.[7] According to the SLR results, for the treatment of oral dryness we do not recommend the use of hydroxychloroquine (no placebo-differences for subjective and objective oral outcomes in the pivotal RCT), oral GCs, immunosuppressive agents (overwhelmingly-negative results with excess side effects) or rituximab (no placebo-differences for subjective and objective oral outcomes in the two pivotal RCT and one meta-analysis)

Saliva substitution

Saliva substitution should be considered the preferred therapeutic approach to alleviate symptoms in patients with no residual glandular function (severe glandular dysfunction), in whom salivary glands cannot be stimulated, either by pharmacological or non-pharmacological interventions (figure 1). The ideal preparation will have a neutral pH and contain fluoride and other electrolytes, mimicking the composition of natural saliva; saliva substitutes are available commercially in the form of oral sprays, gels and rinses.[10] Only one prospective study evaluated pSjS-2002 patients[35] and found no statistically-significant placebo-differences for the primary outcome, although significant improvements were reported in some subjective oral outcomes, with no side effects reported. Evidence can be extrapolated from a Cochrane SLR that evaluated the effectiveness of topical treatments for any-cause dry mouth; the review found no superiority for any therapeutic option.[27] In spite of the limited evidence available, we recommend their use in the target population because, in the experience of TF members, patients often report increased oral comfort without significant side effects.[10] Oral gel-like formulations may be useful in patients with an acceptable salivary flow output, particularly when they complain about nocturnal oral dryness, although these patients often have a poor tolerance to saliva substitutes due to the sticky feeling caused by their application, which may be reduced by diluting the saliva substitute. Pretherapeutic evaluation of salivary function may also aid the choice of a specific formulation of saliva substitutes (gel, saliva substitute—diluted or not,mouth rinses), with less thick/dense preparations being preferred for patients with a better-preserved glandular function.[36] The preferred first-line use of saliva substitutes in patients with no salivary output elicited an intense debate within the TF, probably due to the apparent paradox of using a topical therapy in patients with severe glandular involvement. Several TF members expressed a dissenting view, stating that saliva substitutes should be used in all patients with oral dryness, irrespective of glandular function. Whether or not a saliva substitute is used, a neutral pH sodium fluoride gel should be prescribed to all patients with severe salivary dysfunction to prevent rampant caries.

The first-line therapeutic approach to ocular dryness includes artificial tears and ocular gels/ointments (*LoE 1a, LoA 9.5*)

The first line of therapy for ocular dryness should be volume replacement and lubrication using artificial tears (AT) and ocular gels, whose main ingredients are lubricants with a polymeric base or viscosity agent (methylcellulose, hyaluronate) with the aim of adding volume to the tear lake, increasing the time the AT remain on the ocular surface, and cushioning the ocular surface to reduce friction between lid and globe.[37] All SjS studies testing AT (only one in pSjS-2002 patients) found significant improvements for both subjective and objective ocular outcomes, while a recent Cochrane review on the use of AT for dry eye syndrome showed that they are safe and effective.[28] We recommend that all SjS patients presenting with ocular dryness and/or abnormal ocular tests should use AT containing methylcellulose or hyaluronate at least twice daily, with the frequency increased to as often as hourly, as indicated by symptoms and/or objective signs. The use of preservative-free formulations of AT is mainly recommended in patients requiring four or more applications per day. Ophthalmic ointments are thicker than AT and may be used to provide symptom control overnight; they are typically used before bedtime because they produce blurred vision and their use should be followed by morning lid hygiene to prevent blepharitis.[37]

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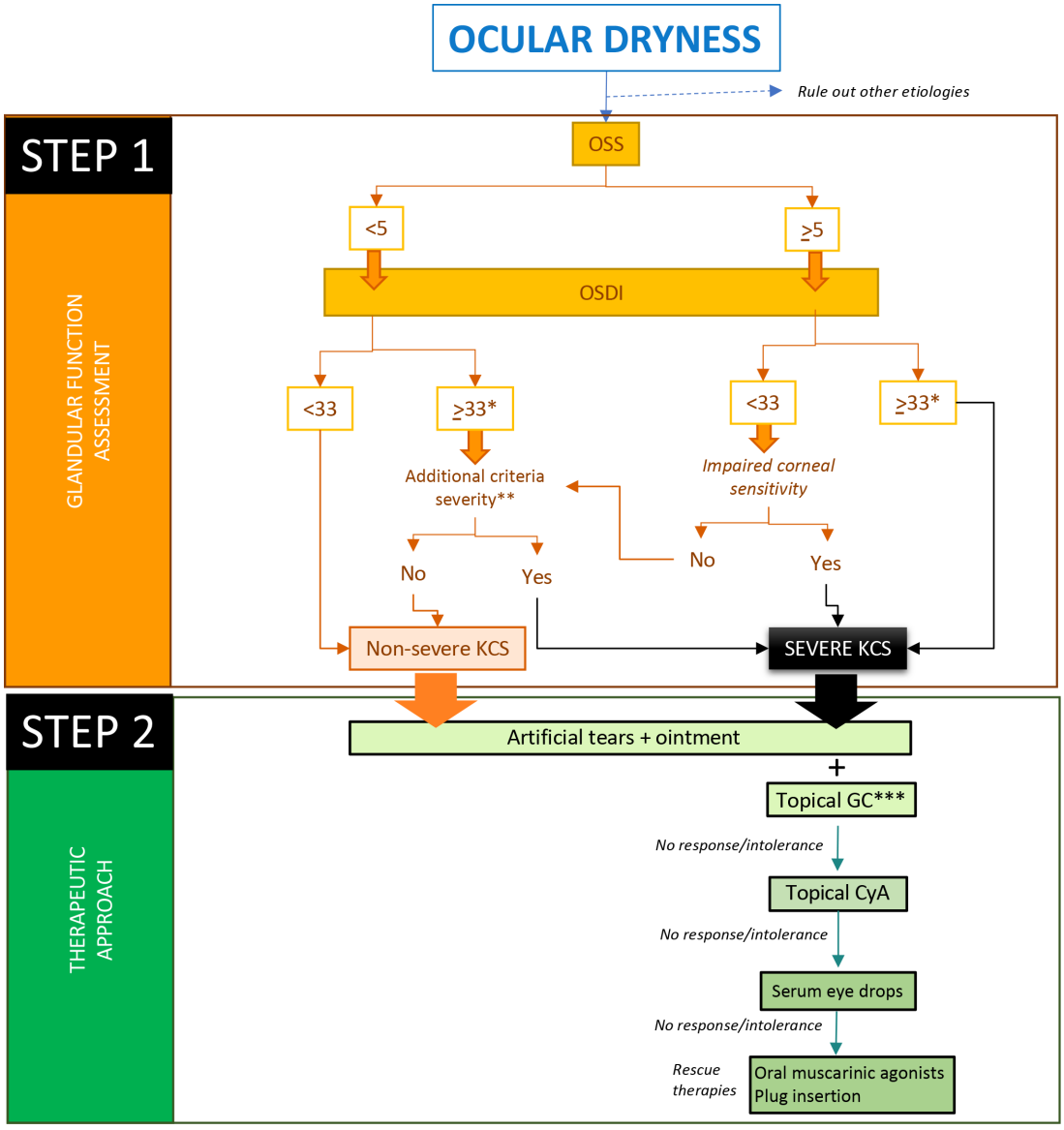

Figure 2 Algorithm of glandular function assessment and therapeutic approach in patients with primary SjS presenting with ocular dryness. *Consider neuropathic pain if OSS≤1. **Additional criteria for severity: (1) impaired visual function (photophobia, visual acuity modification or low contrast sensitivity); (2) blepharospasm (secondary to ocular inflammation); (3) severe meibomian gland disease or eyelid inflammation. ***For short-term indications (2–4 weeks). CyA, ciclosporin A; GC, glucocorticoid; OSS, ocular staining score (Whitcher[107] JP, *et al*. Am J Ophthalmol. 2010;149:405–15). OSDI, ocular surface disease index (adapted from Baudouin C,[108] *et al*. Br J Ophthalmol 2014;98:1168–1176); SjS, Sjögren syndrome.

Refractory/severe ocular dryness may be managed using topical immunosuppressive-containing drops* and serum eye drops (*LoE 1a/*1b, LoA 9.1*)

Patients with refractory or severe ocular dryness should be managed by an ophthalmologist with substantial experience in corneal disease wherever possible. Refractory ocular dryness is defined as patients who do not improve after using the best-available standard of care (SOC) (defined as the maximum use of AT and ointments according to the previous recommendation) after ruling out other SjS-unrelated ocular processes (ie, blepharitis), while severity should be defined according to the results obtained in a specific ophthalmological evaluation of corneal damage by measuring the OSS, together with patient symptoms as assessed by the Ocular Surface Disease Index (figure 2).

Topical NSAIDs/corticosteroids

Topical ocular non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids may be prescribed by ophthalmologists as a short-term therapeutic approach (maximum 2–4 weeks), as adverse events may occur with continued use of topical NSAIDs (corneal–scleral melts, perforation, ulceration and severe keratopathy) or topical corticosteroids (infections, increased intraocular pressure and worsening/development of cataracts).[37] Evidence in pSjS-2002 patients is limited to one small case-control study[38] using topical fluorometholone which found no significant differences in comparison with topical ocular ciclosporin A (CyA).

Topical CyA

In December 2002, an ophthalmic formulation containing 0.05% CyA was approved by the Food and Drug Administration to treat dry eye disease in the USA based on the results of two RCTs including patients with keratoconjunctivitis sicca (SjS patients were included in variable proportions).[7] There are no specific RCTs carried out in pSjS-2002,[39 40] and only one recent case-control study, which reported no significant differences

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between groups in comparison with topical fluorometholone, with a higher frequency of moderate-to-severe transient burning sensation in patients receiving CyA.[38] Ophthalmologists may consider the use of ocular CyA drops in patients with refractory or severe ocular dryness requiring repeated courses of glucocorticoid tear drops. The promising results of a recent small trial using tacrolimus tear drops[41] required further confirmation in large trials.

Serum tear drops

In SjS patients, the role of autologous or allogenic serum has been tested in small uncontrolled studies showing inconsistent benefits (no improvement in all objective ocular outcomes evaluated). A recent Cochrane SLR on the use of serum tear drops for dry eye syndrome[42] has confirmed inconsistencies in their possible benefits both for symptoms and objective measures, with no evidence of an effect after 2 weeks of treatment. Only one study has been carried out in pSjS-2002 patients, which showed significant improvement in some ocular outcomes.[43] The difficulties in preparation, the need to refrigerate the drops, and the potential risk of contamination should be taken into account.[37 44] The TF recommended that serum tear drops may be considered in patients who are non-responders or intolerant to topical CyA tear drops.

Rescue therapies

Other therapeutic interventions may be considered after failure of the above-mentioned therapies, including topical and systemic therapies. A recent Cochrane SLR reviewing the use of plugs for dry eye syndrome[45] found that the evidence was very limited, and concluded that improvements in subjective and objective ocular outcomes were inconclusive. Two studies have been carried out in primary-2002 SjS patients: the first found no significant differences between groups (insertion of plugs vs AT),[46] and the second reported improvement in only two of four ocular outcomes evaluated.[47] With respect to systemic therapies, oral muscarinic agonists may be considered on the basis of the improvement of subjective (not objective) ocular outcomes.[7] According to the SLR results, for the treatment of ocular dryness we do not recommend the use of hydroxychloroquine (no placebo-differences for subjective and objective ocular outcomes in the pivotal RCT), immunosuppressive agents (overwhelmingly negative results with excess side effects) or rituximab (no placebo-differences for subjective and objective oral outcomes in the two pivotal RCT and one meta-analysis).

In summary, although patients with refractory/severe ocular dryness may require a more intensive ophthalmological follow-up and, probably, more complex therapies, including immunosuppressive-based tear drops (topical corticosteroids or CyA) and serum tear drops, the low level of current evidence for the use of these complex ophthalmological therapies in primary SjS-2002 patients do not permit the TF to establish a strong preference among the options. The expertise of the ophthalmologist and the specific characteristics of the patient will drive both the preferred first-line therapy and the sequential use of the therapeutic interventions.

Concomitant diseases should be evaluated in patients presenting with fatigue/pain, whose severity should be scored using specific tools (*LoE 5, LoA 9.0*)

Patients with primary SjS often present with general symptoms, of which most frequent are non-inflammatory joint/muscle pain and fatigue/weakness, which may have a much greater impact on the HRQoL than sicca features, as reported in cross-sectional studies.[23–25] Unfortunately, these symptoms are very unspecific and could be related to a wide range of concomitant pathologies (osteoarthritis, hypothyroidism, hypocortisolism, vitamin deficiencies, depression, neoplasia) and even to some systemic complications of systemic SjS (arthritis, anaemia, hypokalaemia, osteomalacia, lymphoma, small-fibre neuropathy). A specific comment is needed on the association between SjS and some somatic functional syndromes such as chronic fatigue syndrome and fibromyalgia, whose peak of incidence occurs in the same population subset as SjS (middle-aged women).[21] No studies have confirmed a solid aetiopathogenic autoimmune link between SjS and chronic fatigue syndrome/fibromyalgia[48] beyond the evident epidemiological overlap. Since the association of these somatic syndromes could heavily influence both the patient and physician global health status evaluation, we recommend searching for these syndromes using standardised recommendations,[49] and measuring the severity of pain and fatigue using specific scales such as the corresponding ESSPRI domains, the Profile of Fatigue (for measuring fatigue) and the Brief Pain Inventory (for measuring pain).[50] SjS patients may describe various kinds of pain and fatigue, and the use of both general and SjS-specific questionnaires will permit not only a standardised measurement of their potential impact on HRQoL, but consideration of their influence when specific therapeutic interventions are initiated.[10 51]

Consider analgesics or other pain-modifying agents for musculoskeletal pain, taking into account the balance between potential benefits and side-effects (*LoE 4, LoA 8.9*)

With respect to SjS-related musculoskeletal pain, a clear pretherapeutic differentiation must be made clinically between joint pain (arthralgia) and joint inflammation (arthritis, tenosynovitis).[52] The ESSDAI score classifies arthralgia in the hands, wrists, ankles and feet accompanied by morning stiffness (>30 min) as low articular activity level, always ruling out concomitant osteoarthritis. Arthritis is clinically diagnosed on the basis of objective inflammation of ≥1 joints (heat, redness and swelling in the physical examination of the affected joint) supported by ultrasound studies when in doubt, and the ESSDAI score classifies the severity of arthritis according to the number of joints involved (moderate ≤5 joints, high >5).[12] The therapeutic management of arthritis is included in the systemic recommendations. (a) In patients presenting with acute musculoskeletal pain, consider acetaminophen or NSAIDs for symptomatic relief, always for less than 7–10 consecutive days at full dosage and considering the side effects and underlying comorbid diseases. In real life, a large retrospective study in 188 primary 2002 SjS patients with joint involvement reported that nearly one third had a rapid clinical response to the short-term use of analgesics/NSAIDs.[53] Topical formulations of NSAIDs (topical diclofenac or ketoprofen) may be effective for local pain with fewer side effects,[54] but there is no available evidence in SjS patients.[55] (b) In patients with frequent episodes of acute musculoskeletal pain, the use of hydroxychloroquine has been proposed based on its comparable use in other SAD such as systemic lupus erythematosus (SLE). Although uncontrolled studies have reported improvement in joint pain, the pivotal RCT failed to demonstrate that hydroxychloroquine improved pain after 24 weeks of treatment in comparison with placebo, although a statistical trend was reported (p values between 0.06 and 0.10) at 12, 24 and 48 weeks).[56] Taking this positive trend, the lack of reported cases of retinal toxicity or severe adverse events, and the lack of pharmaceutical

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alternatives with a similar indication/safety profile, the TF members agreed to consider the use of hydroxychloroquine in some patients with frequent episodes of articular pain. In real life, the study by Fauchais *et al*[53] reported the use of hydroxychloroquine in more than half the patients presenting with joint involvement. With respect to the use of biological agents to treat these symptoms, the data from the two pivotal RCTs[57 58] on the effect of rituximab on pain and fatigue reported no significant differences in comparison with placebo for both pain and fatigue VAS (although some differences were found at intermediate evaluation points in the French study), together with no significant placebo-differences in quality-adjusted life-year but with a fivefold greater economic cost,[58] while a recent meta-analysis[59] confirmed no significant differences after combining the results of these trials. In addition, a small RCT using anakinra found no significant reduction in fatigue in its primary endpoint,[60] while the promising results obtained in two small open-label studies (<30 patients) using epratuzumab[61] or abatacept[62] must be confirmed in further large RCTs. Therefore, we consider that the off-label use of biological agents to treat only musculoskeletal pain (even as rescue therapy) is not currently warranted. (c) In patients with chronic, daily non-inflammatory pain, the management must be completely different, avoiding the repeated use of NSAIDs or GCs. The non-pharmacological management of pain should be emphasised, instead of going straight to prescribing medications for the symptoms. Therefore, the first therapeutic step should be to follow the same recommendations as those proposed for general chronic pain, by suggesting that physical activity and aerobic exercise are interventions with few adverse events that may reduce pain severity and improve physical function.[63] In addition, a small case-control study in primary SjS patients showed significant improvement in aerobic capacity, fatigue and ratings of perceived exertion and depression in patients allocated to the exercise group.[64] Antidepressants and anticonvulsants may be considered for chronic musculoskeletal pain, while patients with chronic neuropathic pain may require the use of gabapentin, pregabalin or amitriptyline (paying attention to potential exacerbations of dryness symptoms). Recent epidemiological data confirm that opioids must not be used.[65]

Treatment of systemic disease should be tailored to organ-specific severity using the ESSDAI definitions (*LoE 4, LoA 9.0*)

In non-specialised medical settings, primary SjS is often considered a chronic, non-life-threatening disease that only causes dryness, fatigue and pain. However, systemic involvement has been increasingly recognised as a key part of the disease, with a significant weight in dictating the prognosis and survival in retrospective studies.[66–69] The development of the ESSDAI by the EULAR-SS Task Force Group has provided a helpful, objective instrument to measure systemic involvement in primary SjS that is accepted worldwide. According to overarching principle C, we recommend that the use of systemic therapies (GCs, antimalarials, immunosuppressive agents, intravenous immunoglobulins, biologics) should be restricted to patients with active systemic disease (see definitions in table 2). However, the management of systemic features must be tailored to the specific organ involved and the severity evaluated by the ESSDAI.[69] As an overall rule, systemic therapies may be considered for most patients presenting with at least moderate activity in one clinical domain, or with a global moderate disease activity score (score ≥5). With respect to the definition of the therapeutic response in systemic SjS, the TF recommends using a reduction of ≥3 points in the global ESSDAI score.[70] It should also be considered that some systemic manifestations are not captured by the ESSDAI, including Ro-associated congenital heart block, Raynaud phenomenon, primary pulmonary hypertension, pleuritis, pericarditis, dysautonomia, interstitial cystitis and sensorineuronal hearing loss; these features require specific patient-by-patient management.

GCs should be used at the minimum dose and length of time necessary to control active systemic disease (*LoE 4, LoA 9.6*)

The frequent use of GCs in clinical practice in primary SjS patients[69 71 72] is not supported by reliable scientific evidence, since no controlled study has specifically evaluated their use for systemic disease. Available data come mainly from retrospective studies (online supplementary table S2) and case series/reports, which also highlighted the high rate of GC-related adverse events. We recommend that GCs should be used at the minimum dose and length of time necessary to control active systemic disease, administering pulses of methylprednisolone followed by doses of 0.5 mg/kg/d or lower as induction therapy in severe presentations (table 2), and doses<0.5 mg/kg/d in moderate/less-severe presentations, with a final target of withdrawing GCs in inactive patients as soon as possible or at least trying to target a maintenance dose of 5 mg/daily or less with the aid of GC-sparing immunosuppressive agents (see recommendation 'Synthetic immunosuppressive agents should mainly be used as GC-sparing agents, with no evidence supporting the choice of one agent over another (*LoE 4, LoA 8.9*)'). No available data in SjS patients support specific recommendations on the rate of de-escalation of the GC dose, or when a GC-sparing agent should be added, or the length of GC therapy, although we recommend tapering GCs as rapidly as clinically feasible. We recommend to follow the EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases.[73]

Synthetic immunosuppressive agents should mainly be used as GC-sparing agents, with no evidence supporting the choice of one agent over another (*LoE 4, LoA 8.9*)

Based on the potential development of chronic damage in patients with uncontrolled systemic disease, some patients may require long-term therapy with GCs, especially those with severe organ impairments.[69 71 72] In these patients, the addition of immunosuppressive agents as GC-sparing agents is justified, always weighing the potential benefits and risks. The use of immunosuppressive agents in primary SjS is based on the same level of evidence as that of GCs, since all reported studies (prospective uncontrolled studies, all including less than 50 patients) were principally centred on the efficacy in sicca features and laboratory parameters, but not on the efficacy in systemic disease, with an unacceptable rate of adverse events (ranging between 41% and 100%).[7] The lack of head-to-head studies comparing the efficacy and safety profile of immunosuppressive agents in primary SjS-2002 (leflunomide, methotrexate, azathioprine, mycophenolate, cyclophosphamide) does not permit a recommendation on the use of one agent over another, except when patient characteristics or comorbidities are considered with respect to the safety profile. In addition, there is no information available about the dose, route of administration and length of treatment and we recommend a case-by-case evaluation following similar rules to those reported for other SAD. Although some TF members suggested the use of monotherapy with immunosuppressive agents, there was no final consensus on this option due to the lack of studies demonstrating the efficacy

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of GC-free regimens in SjS, and the fact that more than 95% of reported cases using immunosuppressive agents in primary SjS-2002 received associated GCs (online supplementary table S2). Several immunomodulatory agents have been tested in SS, with marginal benefits or with an unacceptable rate of adverse events and are not recommended.[7]

B-cell targeted therapies may be considered in patients with severe, refractory systemic disease (*LoE 1b, LoA 8.6*)

The emergence of biological therapies in this century has increased the therapeutic armamentarium available for treating severe SjS. These new drugs have the highest level of evidence among all the drugs tested for SjS, not only because have they have been tested in a large number of patients (>1000), but also because most of reported RCTs in primary SjS have tested biologics. Unfortunately, their use in clinical practice is clearly limited by the lack of licensing. B-cell targeted therapies are the most frequently tested biological drugs, and include epratuzumab[61] and belimumab,[74 75] although the most widely studied B-cell target therapy is rituximab.[57 58 76–86]

Studies with available data on the efficacy of rituximab on systemic involvement have included more than 400 patients with primary SjS-2002 (online supplementary table S3), with a predominant use of the regimen of 2 doses of 1 g each administered 15 days apart.[7] Four main systemic outcomes were evaluated at different follow-up times in these studies: the global therapeutic response, organ-specific response, change in the global ESSDAI score and reduction in prednisone use. Uncontrolled studies have reported a global response rate of 60%–100% for systemic features, especially cryoglobulinemic features.[76 77 79 80 86] One small RCT[86] reported a significant reduction in reported extraglandular manifestations and improvement of musculoskeletal features at weeks 12 and 36 (p=0.029) and vasculitis at week 24 (p=0.03). Four studies (two retrospective, one case-control and one prospective) have reported a statistically-significant reduction in the global baseline ESSDAI score (from 9 to 20.3 to 2.5–5.2 after treatment).[77–80 84] In the two pivotal RCTs, Devauchelle *et al* found no differences in the mean ESSDAI improvement,[57] while Bowman *et al*[58] reported statistically-significant placebo differences at week 36 (p=0.03) and a statistically-significant trend at week 48 (p=0.07) in the log-transformed ESSDAI score. Three retrospective studies have demonstrated a statistically significant reduction in the daily dose of GCs.[76 79 80] In summary, the great majority of studies showed efficacy in at least one of the systemic outcomes analysed (global response, organ-specific response, ESSDAI reduction, prednisone reduction).

The results of the Efficacy and Safety of Belimumab in Subjects with Primary Sjögren's Syndrome open label trial[74] in 30 pSjS-2002 patients treated with belimumab showed a reduction in the mean ESSDAI score from 8.7 to 5.7 at week 28 (p<0.0001), with a decrease of at least 4 points in 40% of cases and improvements in

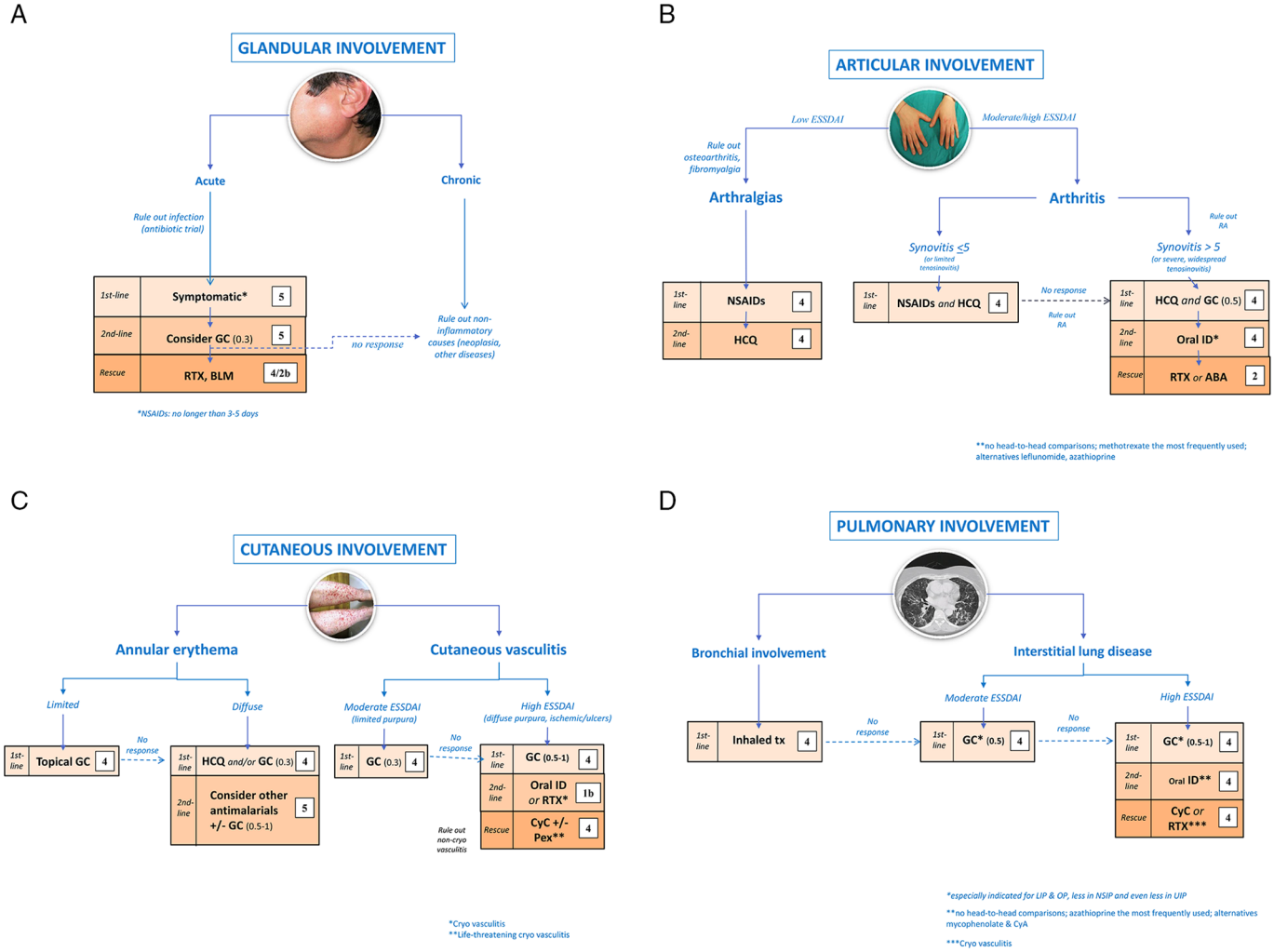

Figure 3 *(Continued)*

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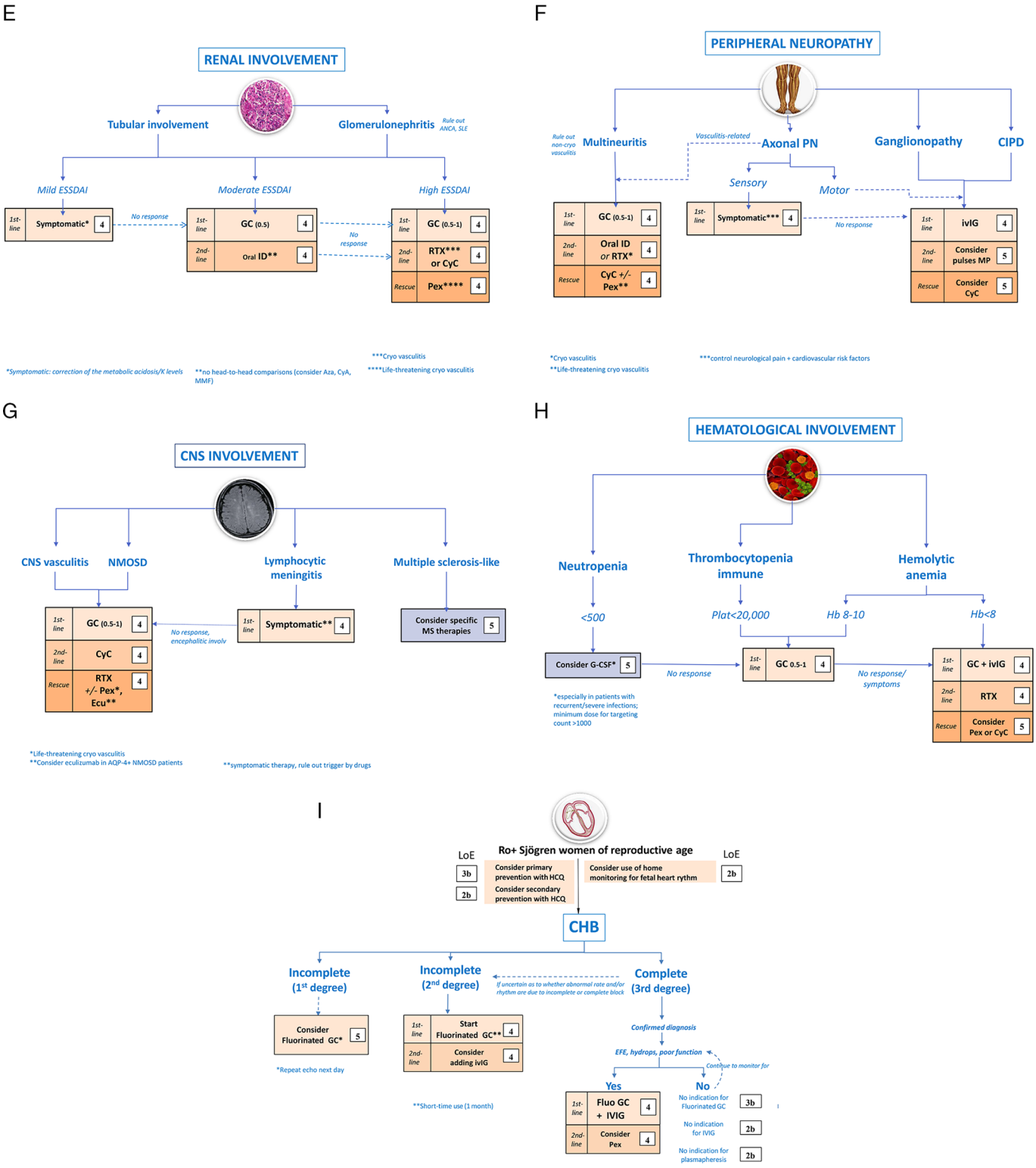

Figure 3 (A to I) Algorithm for the therapeutic approach to patients with primary SjS presenting with organ-specific systemic involvements. NSAIDs: no longer than 7–10 days. HCQ: hydroxychloroquine 200 mg/day. GC (recommended dose in mg/kg/day); short-term course whenever possible; consider methylprednisolone pulses in severe cases. ID: immunosuppressive agents, no head-to-head comparisons. CyC: cyclophosphamide pulses 0.5 g/15 day (maximum six pulses). Rituximab: rituximab 1 g/15 days (x2). BLM: belimumab; 10 mg/kg (0, 2 and 4 weeks and then every 4 weeks). ABA: abatacept 0, 2, 4 weeks and every 4 weeks. IVIg: intravenous immunoglobulins 0.4–2 g/kg 5 days. PEX: plasma exchanges. CyA, ciclosporin A; EULAR, European League Against Rheumatism; ESSDAI, EULAR Sjögren's syndrome disease activity index; GC, glucocorticoid; LoE, levels of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SjS, Sjögren syndrome.

parotid swelling in 77% of cases; of five patients previously refractory to rituximab, belimumab was effective in 3 (60%). In a study extension of the 19 patients that completed 1 year of treatment, a significant improvement was maintained.[75] With respect to the safety profile, one severe adverse event was reported (pneumococcal meningitis) after 6 infusions of belimumab.

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After intense discussion among the TF members and balancing the positive results of uncontrolled studies, the weak evidence reported by RCTs, and the fact that the trials were not primarily designed to evaluate the systemic response, we agreed that the use of rituximab may be considered (we changed the original wording of 'should be') in patients with severe, refractory systemic disease, and that the best indication is probably for symptoms linked to cryoglobulinemic-associated vasculitis,[87] with the possible use of belimumab as rescue therapy.

The systemic organ-specific therapeutic approach may, as a general rule, follow the sequential (or combined) use of GCs, immunosuppressive agents and biologics (*LoE 5, LoA 8.6*)

The recommended general sequential use of the three main categories of immunosuppressive agents in SjS is based on a similar approach to that reported for other SAD such as SLE or vasculitis, with no controlled studies supporting this approach in SjS. As a general rule, for most systemic involvements GCs (see recommendation 'GCs should be used at the minimum dose and length of time necessary to control active systemic disease *(LoE4, LoA9.6)*') may be considered the first-line option in patients with active systemic disease, and immunosuppressive agents and biologics as second/third line options to be used in patients intolerant or refractory to GCs, those with severe disease or those in whom long-term GC use is anticipated. In spite of the greater amount of scientific evidence data available for rituximab in comparison with GCs and immunosuppressive agents, the lack of licensing, the lack of controlled studies for systemic disease and the lack of head-to-head comparisons between rituximab and classic immunosuppressants (especially with respect to the safety profile) were issues to be considered. After an intense discussion among the TF members, the TF agreed to merge the two options as second-line therapies (adding a specific note about the use of rituximab as especially recommended for associated cryoglobulinemic vasculitis), always with a careful case-by-case assessment of the use of rituximab in an off-label context, evaluating potential benefits and adverse effects patient-by-patient (table 2), and taking into account the fact that their use will depend on drug availability and national regulations.

Unfortunately, after analysing the available evidence, no controlled data was identified to support a differentiated organ-guided therapeutic approach for systemic SjS, and some TF members recommend no strictly adherence to sequential therapy management, with an individualised therapeutic approach being preferable. However, on the basis of the results, principally from retrospective studies (online supplementary table S2), together with the clinical experience of the TF members, a list of consensus-based algorithms defining SOC and second/third line therapies was proposed for each clinical ESSDAI domain (figure 3A–I); Ro-associated congenital heart block (not included in the ESSDAI) was also included due to its prognostic significance. There was no consensus on the proposal to make recommendations for organ-specific maintenance therapeutic regimens.

Treatment of B-cell lymphoma should be individualised according to the specific histological subtype and disease stage (*LoE 4, LoA 9.7*)

Among the systemic manifestations of SjS, lymphoma is one of the worst complications, with standardised incidence ratios for B-cell lymphoma ranging between 7 and 9 in population-based studies and between 16 and 48 in hospital-based studies.[88] Although the vast majority of cells infiltrating the salivary glands of patients with primary SjS are T cells, the majority of lymphomas reported are of B-cell origin with a ratio between B and T-cell lymphomas of 15:1; three subtypes of B-cell lymphoma account for more than 90% of reported cases in primary SjS: mucosa-associated lymphoid tissue (MALT) lymphoma, other marginal zone lymphomas (MZL) and Diffuse large B cell lymphoma.[88] Following the diagnosis of lymphoma, therapy should be individualised according to the specific histological subtype defined according to the WHO 2016 classification[89] and the corresponding current therapeutic guidelines, with a personalised therapeutic approach driven by the haematologist/oncologist. For primary SjS-2002 patients diagnosed with low grade haematological neoplasia, some clinicians recommend a watchful waiting approach when lymphoma only affects the exocrine glands,[90] especially in the absence of constitutional symptoms, systemic features or B-cell activation biomarkers.[3] The decision to treat low-grade lymphomas or not must be discussed in a multidisciplinary committee, taking into account the fact that they are linked to the disease activity and are the ultimate stage of autoimmune B-cell activation. Moreover, low grade B-cell lymphomas have a potential risk of progression to more aggressive types of lymphoma.[3] In patients with disseminated MALT lymphoma or with concomitant high disease activity, chemotherapy may be considered on a case-by-case basis.[3] For patients with marginal zone lymphomas, small lymphocytic lymphoma (SLL) and lymphoplasmacytic lymphoma (LPL) in early disease stages (in particular, stage I or non-bulky stage II), treatment may include radiotherapy (with or without chemotherapy), although a watch-and-wait strategy could be an alternative to spare the side effects of therapy.[91] For patients with moderate/high grade haematological neoplasia, treatment is based on standard rituximab-based chemotherapy regimens. The benefit of adding rituximab to chemotherapy has been demonstrated in a meta-analysis in patients with follicular lymphomas, mantle cell lymphomas and other indolent lymphomas.[91] Rituximab plus fludarabine or bendamustine (BR) are the recommended first-line therapy for MZL, SLL and LPL; a recent study in 13 patients with pSjS-2002 (77% stage IV) complicated by MZL has reported the efficacy of the BR combination in all 13 cases, with improvement in the other SjS non-lymphomatous manifestations and with a good safety profile.[92]

DISCUSSION

The EULAR recommendations for the management of SjS with topical and systemic therapies management have been developed by a large, multidisciplinary, multiprofessional team. In summary, nine RCTs (only three including 120–130 patients), 18 prospective (all including between 10 and 50 patients) and five case-control studies were selected to support the scientific evidence presented here. This is a small number of studies that is not comparable with rheumatoid arthritis (RA) or with other, more closely-related diseases, such as SLE or systemic vasculitis. Therefore, the evidence accumulated in this century reveals SjS as a true orphan disease from a therapeutic point of view,[59 93] with the absence of any efficacious agent, a situation that is in clear contrast with the significant advances achieved in both basic and clinical research during this period. As a consequence of the limited evidence available, therapeutic decisions in daily practice are often based on a mix of reported expert opinions and personal experience, which may vary widely between countries: therefore, the present recommendations are based on the input of experts from 16 European countries and wide international representation from the other continents. In addition, SjS presents with a wide range of signs and symptoms (not only the

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key features of dryness, fatigue and pain, but also those derived from organ-specific systemic involvements and lymphoma), with a large number of different specialties involved and, therefore, with a wide variety of potential interventions. Methodologically, we have also taken into account the continuous changes in classification criteria since 1986 and, in consequence, the continuous changes in the target population classified as primary SjS. For this reason, we decided, in the Population, Intervention, Comparison, Outcomes and Study design strategy, to focus on the evidence collected from therapeutic studies including pSjS-2002 patients, since these criteria have been used for a longer and more-recent period and because of their similarity with the recent 2016 American College of Rheumatology (ACR)/EULAR criteria.[16]

In SjS, we are very far from the 'disease modification' concept as the mainstay of treatment (as used in other diseases such as RA, a concept that allows the use of the term disease modifying antirheumatic drugs for many drugs that have demonstrated the ability to prevent structural damage progression in RA). A rapid overview of the LoE that support each statement (table 1) shows that all recommendations for managing oral and ocular dryness are principally supported by evidence extrapolated from Cochrane SLRs that evaluated their management in mixed aetiological populations; on the management/prevention of dryness-related complications (oral ulcers, candidiasis, caries/dental complications, ocular infections), the management of dryness other than oral or ocular, or the role of non-therapeutic interventions in dryness, there was a very limited number of studies carried out in 2002 primary SjS patients, and we recommend following published guidelines.[9–11 37 94] With respect to the most frequently used synthetic drugs (GCs and immunosuppressive agents), the available evidence came from isolated uncontrolled studies. The only exceptions were for hydroxychloroquine and rituximab, which were both tested in well-designed RCTs, although there were no statistically-significant differences with respect to placebo for the primary outcome (efficacy in dryness, fatigue and pain). With respect to systemic disease, the use of rituximab was supported by a large number of studies, mainly uncontrolled. We are also very far from defining specific treatment targets (especially searching for remission in non-systemic features), but it may be useful to use the EULAR disease activity states,[70] considering that any higher disease activity has to be regarded as inadequate disease control, thus mandating a therapeutic intervention, or that low disease activity achieved after therapy may be potentially acceptable for some organs. In any case, as stated in previous EULAR recommendations,[95] communication with the patient to clarify and agree on the treatment goal and the means to attain it is of utmost importance. Monitoring should be frequent in patients with systemic active disease, although the frequencies of follow-up examinations should be adjusted in accordance with the individual disease activity state,[70] namely, more frequently, such as monthly, when patients have high disease activity, and less frequently, such as every 6–12 months, when patients have low disease activity.

Lessons should be learnt from the first biological tested in primary SjS (infliximab). The excellent results of tumour necrosis factor-targeted therapies in RA led to their testing in patients with primary SjS, in spite of the large pathological and clinical differences between the two diseases. After the report of promising results in small open-label studies (one of which has been recently retracted by the authors), the first well-designed RCT showed no differences between the infliximab and placebo arms for the primary outcome. The same disappointing results have been obtained for other drugs reported as efficacious according to uncontrolled data (hydroxychloroquine and rituximab) without significant results for the primary outcomes when tested in RCTs. In SjS trials, two common issues may help to explain the negative results. The first is the choice of primary end-points. Most studies used composite primary outcomes based mainly on the subjective evaluation of dryness, fatigue, pain[96] ; the strong influence of personal and environmental factors on the intensity of this triad of symptoms could explain the lack of significant differences (a higher rate of placebo-related response), together with inadequate patient selection (too low degree of disease activity), the influence of concomitant drugs and the heterogeneity of diagnostic tests. The composite ESSDAI to measure systemic activity was used in the most recent RCT as a secondary end-point and frequently calculated retrospectively (although one of the weaknesses of this outcome could be the difficulty in differentiating activity due to chronic damage in different domains). The preliminary results of two new RCTs where ESSDAI was the primary end-point demonstrated efficacy of the active drug versus placebo (anti-CD40 and the combination of leflunomide and hydroxychloroquine).[97 98] The second issue is the limited number of patients randomised (no more than 50–60 patients per arm), taking into account the clinical and immunological heterogeneity of SjS as an SAD (such as SLE or systemic vasculitis); in SLE, the pivotal trials that allowed the licensing of belimumab were obtained from two trials including nearly 1000 patients each. Some promising results recently reported in small open-label studies testing biologics (belimumab, anakinra) must be confirmed in further large well-designed RCTs, while advance results of a large trial in primary SjS do not indicate a clinical benefit of abatacept.[99] The current therapeutic pipeline in SjS, as shown by the *clinicaltrials.gov* webpage, is that the biologic therapeutic approach overwhelmingly used in SjS until now (targeting B-cell depletion) is shifting towards the evaluation of biologics targeting cytokines, T-cells and intracellular signalling pathways.[100] With respect to ongoing trials, considerable interest is centred on the B cell survival factor (BAFF) pathway, investigating the effect of monoclonal antibodies targeting BAFF-receptor or the association between B-cell depletion and BAFF inhibition. In addition, studies are testing inhibition of other pathways activating B cells. Lastly, four ongoing trials are testing other pathways or the use of other cytokine-based therapies including tocilizumab, abatacept, filgotinib (a janus kinase inhibitor) and human recombinant Il-2.

Therapeutic research in SjS should probably be reconsidered in order to explore new pathogenic targets outside the glandular tissue (ie, neuroendocrine pathways), and to search for a more personalised therapeutic approach based on genetic, clinical, immunological and/or histopathological characteristics. It is not improbable that future RCTs would benefit from more selected patient cohorts, possibly including newly diagnosed SjS patients, the findings of early salivary gland ultrasound changes,[101–103] or evidence of early high disease activity at diagnosis[22] before permanent damage has been established and the changes are still reversible. Patients with sicca-limited disease differ from those with systemic disease, as do immune-negative patients from those carrying Ro autoantibodies or cryoglobulins, while recent etiopathogenic studies are beginning to divide SjS patients according to the genetic profile between those with or without a predominant IFN-I gene expression signature.[104–106] Sensitivity analyses searching for a differentiated response to therapies in these subsets of patients (sicca-limited vs systemic; Ro+ vs Ro-; positive vs negative salivary gland biopsy; positive vs negative IFN-I signature) might help to better delineate the therapeutic effect of a drug tested in primary SjS, although this would require

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Box 1 Research agenda

- Is there a specific, differentiated treatment of lymphomas related to SjS?
- Is combination therapy a potential intervention to explore in SjS?
- Exploring targeted therapies against Th17 cytokines, IFNα, RORγt expression, Janus kinases (JAKS), STATs and mTOR intracellular pathways or interleukin-1.
- Searching for predictive factors of biological response.
- Potential use of sequential or intralesional use of biological therapies.
- Encouraging the development of new and innovative therapies.
- In what proportion of systemic patients is induction therapy with current therapeutic options effective in inducing sustained remission?
- Is the use of immunosuppressive and biologic agents safe and efficacious in the absence of concomitant glucocorticoid treatment?
- How safe and efficacious is the off-label use of other biologics after rituximab has failed?
- Can we find predictors of differential response to the synthetic and biological drugs used in SjS?
- Can we predict who will maintain remission after withdrawal of glucocorticoids?
- Will we be able to develop precision (personalised, stratified) medicine approaches in SjS? (IFN signature +/-; immunological or histopathological markers +/-)?
- Which biomarkers will help identify better predictors of poor outcomes?

a greater number of patients randomised than those included in reported trials.

In conclusion, the 2019 EULAR recommendations are based on the recent evidence collected on the management of primary SjS patients and on discussions by a large, broadly-based international TF. The recommendations synthesise current thinking on SjS treatment in a set of overarching principles and recommendations. These have been informed by a specific SLR on the efficacy and safety of topical and systemic interventions, although the high-quality scientific evidence focused on primary SjS patients fulfilling the currently-accepted sets of criteria was limited. However, the TF is convinced that adhering to these recommendations, including shared decision-making, assessing disease activity regularly with the ESSDAI instrument, and applying the sequence of drugs as proposed, will improve overall outcomes in a clear majority of patients with SjS. New research information on treatment strategies, predictive markers and other aspects will soon become available and will probably require an update of the recommendations in coming years (see Future Agenda box 1). Until then, we hope that the current recommendations will be broadly applied in clinical practice and/or serve as a template for national societies to develop local recommendations.

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Empowering Rheumatology Professionals

SPECIAL ARTICLE

2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the health care provider in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To update evidence-based recommendations for the treatment of patients with ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (SpA).

Methods. We conducted updated systematic literature reviews for 20 clinical questions on pharmacologic treatment addressed in the 2015 guidelines, and for 26 new questions on pharmacologic treatment, treat-to-target strategy, and use of imaging. New questions addressed the use of secukinumab, ixekizumab, tofacitinib, tumor necrosis factor inhibitor (TNFi) biosimilars, and biologic tapering/discontinuation, among others. We used the Grading of Recommendations, Assessment, Development and Evaluation methodology to assess the quality of evidence and formulate recommendations and required at least 70% agreement among the voting panel.

Results. Recommendations for AS and nonradiographic axial SpA are similar. TNFi are recommended over secukinumab or ixekizumab as the first biologic to be used. Secukinumab or ixekizumab is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi. TNFi, secukinumab, and ixekizumab are favored over tofacitinib. Co-administration of low-dose methotrexate with TNFi is not recommended, nor is a strict treat-to-target strategy or discontinuation or tapering of biologics in patients with stable disease. Sulfasalazine is recommended only for persistent peripheral arthritis when TNFi are contraindicated. For patients with unclear disease activity, spine or pelvis magnetic resonance imaging could aid assessment. Routine monitoring of radiographic changes with serial spine radiographs is not recommended.

Conclusion. These recommendations provide updated guidance regarding use of new medications and imaging of the axial skeleton in the management of AS and nonradiographic axial SpA.

INTRODUCTION

Axial spondyloarthritis (SpA), comprising ankylosing spondylitis (AS) and nonradiographic axial SpA, is the main form of chronic inflammatory arthritis affecting the axial skeleton (1). AS affects 0.1–0.5% of the population, and is characterized by inflammatory back pain, radiographic sacroiliitis, excess spinal bone formation, and a high prevalence of HLA–B27 (2,3). Although nonradiographic axial SpA shares several features with AS, advanced sacroiliac joint damage and spine ankylosis are absent (4). The severity of arthralgia, stiffness, and limited flexibility varies widely among patients and over the course of axial SpA. Skeletal disease may be accompanied by uveitis, psoriasis, and inflammatory bowel disease (IBD). Axial SpA can impose substantial physical and social burdens on patients, and can interfere with work and schooling (5,6). The goals of treatment are to alleviate symptoms, improve functioning, maintain the ability to work, decrease disease complications, and forestall skeletal damage as much as possible.

In 2015, the American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) published recommendations for the treatment of adults with AS and those with nonradiographic axial SpA (7). Recommendations were provided for pharmacologic treatment, rehabilitation, use of surgery, management of selected comorbidities, disease monitoring, patient education, and preventive care. The recommendations were tailored to patients with either active or stable disease and focused on the most common decisions confronting clinicians when treating these patients.

The advent of new medications to treat axial SpA warranted this update. We did not reexamine all of the 2015 recommendations, but rather focused on those questions for which consequential new evidence was present. We added several new recommendations on how the newly available medications should fit in treatment strategies and on the use of imaging. The target populations are adults with AS or nonradiographic axial SpA. The target users of these recommendations are rheumatologists, primary care clinicians, physiatrists, physical therapists, and others providing care to patients with axial SpA.

METHODS

These recommendations followed ACR and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology (8,9), as described in Supplementary Appendix 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract. Briefly, systematic literature reviews were done for prespecified clinical population, intervention, comparator, outcomes (PICO) questions. The resulting evidence was reviewed, and recommendations formulated and voted on, by an expert voting panel (see Supplementary Appendices 2–5 at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Key definitions, including ones for active and stable disease, are provided in Table 1. Clinical trials of ixekizumab became available during the time the manuscript was in preparation, after the voting panel had met (10,11). The data from these trials were provided to the voting panel, and revised recommendations that included ixekizumab were reviewed and voted on by the panel.

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Table 1. Definitions of key terms*

Term	Definition
Active disease	Disease causing symptoms at an unacceptably bothersome level to the patient and judged by the examining clinician to be due to inflammation.
Stable disease	Disease that was asymptomatic or causing symptoms but at an acceptable level as reported by the patient. A minimum of 6 months was required to qualify as clinically stable.
Primary nonresponse	Absence of a clinically meaningful improvement in disease activity over the 3 to 6 months after treatment initiation, not related to toxicity or poor adherence.
Secondary nonresponse	Recurrence of ankylosing spondylitis activity, not due to treatment interruption or poor adherence, after having a sustained clinically meaningful improvement on treatment (generally, beyond the initial 6 months of treatment).
Conventional synthetic antirheumatic drug	Sulfasalazine, methotrexate, leflunomide, apremilast, thalidomide, pamidronate.
Biosimilar	Biopharmaceuticals that are copies of an original biologic medication and tested to be of the same purity and potency as the original. In these recommendations, we refer only to TNFi biosimilars. Examples include infliximab-dyyb, etanercept-szzs, and adalimumab-atto.
TNFi	Infliximab, etanercept, adalimumab, certolizumab, golimumab, and their biosimilars.
TNFi monoclonal antibodies	Infliximab, adalimumab, certolizumab, golimumab.
Biologics	TNFi, abatacept, rituximab, sarilumab, tocilizumab, ustekinumab, secukinumab, ixekizumab.**
High-quality evidence	Studies that provide high confidence in the effect estimate, and new data from future studies are thought unlikely to change the effect.
Moderate-quality evidence	Studies that provide confidence that the true effect is likely to be close to the estimate but could be substantially different.
Low-quality evidence	Studies that provide limited confidence about the effect, and the true effect may be substantially different from the estimate.
Very low-quality evidence	Studies that provide very little certainty about the effect, and the true effect may be quite different from the estimate.
Strong recommendation	Action should be favored in almost all patients, usually requiring high-quality evidence, high confidence that future research will not alter the conclusion, AND an assessment that the desirable effects of the intervention outweigh the undesirable effects. Should not be taken to imply that the intervention has large clinical benefits.
Conditional recommendation	Action should be followed in only selected cases, often limited by low-quality evidence, OR when the desirable and undesirable consequences of an intervention are more balanced, OR if patients' preferences for the intervention are thought to vary widely.
Patient preferences	Beliefs and expectations regarding potential benefits and harms of treatment and how these relate to an individual's goals for health and life.
Shared decision-making	The process by which a patient and clinician arrive at an individualized treatment decision based on an understanding of the potential benefits and risks of available treatment options and of a patient's values and preferences.

* TNFi = tumor necrosis factor inhibitor.

RESULTS

Here we present the recommendations that were reviewed in this update, whether it was a new recommendation (designated "new") or reevaluation of an existing recommendation. Table 2 and Table 3 provide all current recommendations, including those from the 2015 report that were not newly reviewed. The order of recommendations presented here does not imply priority for use or recommended sequencing of different interventions. PICO numbers following each recommendation can be used to locate related evidence in Supplementary Appendix 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract.

**Correction added on 26 September 2019, after first online publication: Secukinumab and ixekizumab were omitted in Table 1. They have been restored in this version of the article.

A. Recommendations for the treatment of patients with active AS

In adults with active AS, we conditionally recommend continuous treatment with nonsteroidal antiinflammatory drugs (NSAIDs) over on-demand treatment with NSAIDs (PICO 1).

The efficacy of NSAIDs for symptom improvement in active AS has been established in many controlled trials. Evidence that continuous NSAID use results in slower rates of spinal fusion on radiographs over 2 years compared to on-demand NSAID use is inconsistent, with results of one trial of celecoxib suggesting less progression with continuous use, and one trial of diclofenac indicating no difference in progression (12,13) (See Supplementary Appendix 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Despite the

Table 2. Recommendations for the treatment of adults with AS*

Recommendation	Level of evidence	PICO
RECOMMENDATIONS FOR ADULTS WITH ACTIVE AS		
1. We strongly recommend treatment with NSAIDs over no treatment with NSAIDs.†	Low	2
2. We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs.	Low to moderate	1
3. We do not recommend any particular NSAID as the preferred choice.†	Low to moderate	3
4. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications. Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNFi are not available.	Very low to moderate	7
5. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib.	Very low	60
6. In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi.	High	6
7. We do not recommend any particular TNFi as the preferred choice.	Moderate	5
8. In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab.	High	58
9. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.	Very low	59
10. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.	Very low	61
11. In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib.	Low	8
12. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary nonresponse to TNFi.	Very low	10
13. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary nonresponse to TNFi.	Very low	10
14. In adults with active AS despite treatment with the first TNFi used, we strongly recommend against switching to treatment with a biosimilar of the first TNFi.	Very low	62
15. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a new biologic.	Very low	9
16. We strongly recommend against treatment with systemic glucocorticoids.†	Very low	4
17. In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.†	Very low	13
18. In adults with stable axial disease and active enthesitis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided.†	Very low	14
19. In adults with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.†	Very low	15
20. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Moderate	16
21. We conditionally recommend active physical therapy interventions (supervised exercise) over passive physical therapy interventions (massage, ultrasound, heat).†	Very low	17
22. We conditionally recommend land-based physical therapy interventions over aquatic therapy interventions.†	Moderate	18
RECOMMENDATIONS FOR ADULTS WITH STABLE AS		
23. We conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs.	Low to moderate	1
24. In adults receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone compared to continuing both treatments.	Very low	11
25. In adults receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing both treatments.	Very low	12
26. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.	Very low to low	66

(Continued)

Table 2. (*Cont'd*)

Recommendation	Level of evidence	PICO
27. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.	Very low to low	65
28. In adults receiving treatment with an originator TNFi, we strongly recommend continuing treatment with the originator TNFi over mandated switching to its biosimilar.	Very low	63
29. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Low	19
RECOMMENDATIONS FOR ADULTS WITH ACTIVE OR STABLE AS		
30. In adults receiving treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate.	Low	64
31. We conditionally recommend advising unsupervised back exercises.†	Moderate	20
32. We conditionally recommend fall evaluation and counseling.†	Very low	51
33. We conditionally recommend participation in formal group or individual self-management education.†	Moderate	48
34. In adults with spinal fusion or advanced spinal osteoporosis, we strongly recommend against treatment with spinal manipulation.†	Very low	21
35. In adults with advanced hip arthritis, we strongly recommend treatment with total hip arthroplasty over no surgery.†	Very low	25
36. In adults with severe kyphosis, we conditionally recommend against elective spinal osteotomy.†	Very low	26
RECOMMENDATIONS FOR ADULTS WITH AS-RELATED COMORBIDITIES		
37. In adults with acute iritis, we strongly recommend treatment by an ophthalmologist to decrease the severity, duration, or complications of episodes.†	Very low	27
38. In adults with recurrent iritis, we conditionally recommend prescription of topical glucocorticoids over no prescription for prompt at-home use in the event of eye symptoms to decrease the severity or duration of iritis episodes.†	Very low	28
39. In adults with recurrent iritis, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics.	Low	29
40. In adults with inflammatory bowel disease, we do not recommend any particular NSAID as the preferred choice to decrease the risk of worsening of inflammatory bowel disease symptoms.†	Very low	31
41. In adults with inflammatory bowel disease, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics.	Very low	32
DISEASE ACTIVITY ASSESSMENT, IMAGING, AND SCREENING		
42. We conditionally recommend the regular-interval use and monitoring of a validated AS disease activity measure.†	Very low	54
43. We conditionally recommend regular-interval use and monitoring of CRP concentrations or ESR over usual care without regular CRP or ESR monitoring.†	Very low	55
44. In adults with active AS, we conditionally recommend against using a treat-to-target strategy using a target of ASDAS <1.3 (or 2.1) over a treatment strategy based on physician assessment.	Low	67
45. We conditionally recommend screening for osteopenia/osteoporosis with DXA scan over no screening.†	Very low	49
46. In adults with syndesmophytes or spinal fusion, we conditionally recommend screening for osteoporosis/osteopenia with DXA scan of the spine as well as the hips, compared to DXA scan solely of the hip or other non-spine sites.†	Very low	50
47. We strongly recommend against screening for cardiac conduction defects with electrocardiograms.†	Very low	52
48. We strongly recommend against screening for valvular heart disease with echocardiograms.†	Very low	53
49. In adults with AS of unclear activity while on a biologic, we conditionally recommend obtaining a spinal or pelvis MRI to assess activity.	Very low	68
50. In adults with stable AS, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity.	Very low	69
51. In adults with active or stable AS on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach.	Very low	70

* AS = ankylosing spondylitis; PICO = population, intervention, comparison, and outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ASDAS = Ankylosing Spondylitis Disease Activity Score; DXA = dual x-ray absorptiometry; MRI = magnetic resonance imaging.
† These recommendations were from 2015 and were not reviewed in this update. The number preceding the recommendation is the recommendation number and is referenced as bracketed numbers in Figure 1.

Table 3. Recommendations for the treatment of adults with nonradiographic axial SpA*

Recommendation	Level of evidence	PICO
RECOMMENDATIONS FOR ADULTS WITH ACTIVE NONRADIOGRAPHIC AXIAL SpA		
52. We strongly recommend treatment with NSAIDs over no treatment with NSAIDs.†	Very low	34
53. We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs.	Very low	33
54. We do not recommend any particular NSAID as the preferred choice.†	Very low	35
55. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications.	Very low	39
56. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi.	High	38
57. We do not recommend any particular TNFi as the preferred choice.	Very low	37
58. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib.	Very low	73
59. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab.	Very low	71
60. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.	Very low	72
61. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.	Very low	74
62. In adults with active nonradiographic axial SpA despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib.	Very low	40
63. In adults with active nonradiographic axial SpA and primary nonresponse to the first TNFi used, we conditionally recommend switching to secukinumab or ixekizumab over switching to a different TNFi.	Very low	42
64. In adults with active nonradiographic axial SpA and secondary nonresponse to the first TNFi used, we conditionally recommend switching to a different TNFi over switching to a non-TNFi biologic.	Very low	42
65. In adults with active nonradiographic axial SpA despite treatment with the first TNFi used, we strongly recommend against switching to the biosimilar of the first TNFi.	Very low	75
66. In adults with active nonradiographic axial SpA despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a different biologic.	Very low	41
67. We strongly recommend against treatment with systemic glucocorticoids.†	Very low	36
68. In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with local glucocorticoids over no treatment with local glucocorticoids.†	Very low	45
69. In adults with active enthesitis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided.†	Very low	46
70. In adults with active peripheral arthritis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.†	Very low	47
71. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Low	22
72. We conditionally recommend active physical therapy interventions (supervised exercise) over passive physical therapy interventions (massage, ultrasound, heat).†	Very low	23
73. We conditionally recommend land-based physical therapy interventions over aquatic therapy interventions.†	Very low	24
RECOMMENDATIONS FOR ADULTS WITH STABLE NONRADIOGRAPHIC AXIAL SpA		
74. We conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs.	Very low	33
75. In adults receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone compared to continuing both medications.	Very low	43
76. In adults receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing treatment with both medications.	Very low	44
77. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.	Low	79
78. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.	Very low	78
79. In adults receiving treatment with an originator TNFi, we strongly recommend continuation of treatment with the originator TNFi over mandated switching to its biosimilar.	Very low	76

(Continued)

Table 3. (*Cont'd*)

Recommendation	Level of evidence	PICO
RECOMMENDATIONS FOR ADULTS WITH ACTIVE OR STABLE NONRADIOGRAPHIC AXIAL SpA		
80. In adults receiving treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate.	Low	77
DISEASE ACTIVITY ASSESSMENT AND IMAGING		
81. We conditionally recommend the regular-interval use and monitoring of a validated AS disease activity measure.†	Very low	56
82. We conditionally recommend regular-interval use and monitoring of the CRP concentrations or ESR over usual care without regular CRP or ESR monitoring.†	Very low	57
83. In adults with active nonradiographic axial SpA, we conditionally recommend against using a treat-to-target strategy using a target of ASDAS <1.3 (or 2.1) over a treatment strategy based on physician assessment.	Very low	80
84. In adults with nonradiographic axial SpA of unclear activity while on a biologic, we conditionally recommend obtaining a pelvis MRI to assess activity.	Very low	81
85. In adults with stable nonradiographic axial SpA, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity.	Very low	82
86. In adults with active or stable nonradiographic axial SpA on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach.	Very low	83

* SpA = spondyloarthritis; PICO = population, intervention, comparison, and outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor; AS = ankylosing spondylitis; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ASDAS = Ankylosing Spondylitis Disease Activity Score; MRI = magnetic resonance imaging.
† These recommendations were from 2015 and were not reviewed in this update. The number preceding the recommendation is the recommendation number and is referenced as bracketed numbers in Figure 1.

uncertainty regarding potential disease-modifying effects, the committee conditionally favored continuous use of NSAIDs in patients with active AS, primarily for controlling disease activity. The decision to use NSAIDs continuously may vary depending on the severity of symptoms, patient preferences, and comorbidities, particularly gastrointestinal and kidney comorbidities, and cardiovascular disease.

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications (new, PICO 7). Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when tumor necrosis factor inhibitors (TNFi) are not available.

Treatment with sulfasalazine is recommended primarily for patients with prominent peripheral arthritis and few or no axial symptoms. However, TNFi may provide a better option for these patients. Evidence for the efficacy of sulfasalazine is based on 8 older controlled trials that showed benefit for peripheral arthritis (see Supplementary Appendix 6, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Although a recent placebo-controlled trial of sulfasalazine demonstrated improvement in axial symptoms, and modest clinical and imaging responses were seen in a second trial, the preponderance of evidence indicates that sulfasalazine has little benefit for axial symptoms (14,15). Sulfasalazine may have a role in treating patients who have contraindications to TNFi, those who decline treatment with TNFi, or those with limited access to TNFi.

Three trials of methotrexate with negative results tested doses of ≤10 mg weekly, and the lack of benefit may reflect the low doses used (16–18). One uncontrolled study of methotrexate 20 mg weekly showed no improvement in axial symptoms, but a decrease in swollen joint count (19). Treatment with methotrexate may be considered for patients with predominately peripheral arthritis, although among nonbiologics, there is more evidence supporting the use of sulfasalazine.

A phase II study of tofacitinib showed benefit in both clinical and imaging outcomes of axial disease over 12 weeks (20). Use of tofacitinib could be another option, although the results of phase III trials are not available. Leflunomide, apremilast, thalidomide, and pamidronate are not recommended (See Supplementary Appendix 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract).

In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi (PICO 6).

In adults with active AS despite treatment with NSAIDs, we do not recommend any particular TNFi as the preferred choice (PICO 5).

The efficacy of TNFi in patients with active AS has been demonstrated in 24 randomized controlled trials, most of which were short-term (6 months or shorter) placebo-controlled studies. Improvements were shown in patient-reported outcomes, composite response criteria, and spine and sacroiliac inflammation on magnetic resonance imaging (MRI) (see Supplementary Appendix 6, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). The panel judged that the evidence justified a strong recommenda-

tion for use of TNFi in patients whose AS remained active (as defined in Table 1) despite treatment with NSAIDs. The panel recommended that lack of response (or intolerance) to at least 2 different NSAIDs at maximal doses over 1 month, or incomplete responses to at least 2 different NSAIDs over 2 months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with TNFi.

Indirect comparisons in network meta-analyses of clinical trials have not showed clinically meaningful differences in short-term efficacy among TNFi in the treatment of active AS (see Supplementary Appendix 6, at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract) (21). Direct comparisons among these medications are limited to a trial of infliximab versus its biosimilar, and a very small open-label trial of infliximab versus etanercept (22,23). The panel judged that the evidence did not support preference of 1 TNFi over any other for the typical patient. Important exceptions apply to patients with recurrent uveitis or coexistent IBD (see PICO 29 and PICO 32 below). Patients treated with infliximab may have increased risks of tuberculosis and of infections generally (24,25). TNFi other than infliximab should be considered for patients at higher risk of tuberculosis exposure (either through travel or household contacts) or with a history of recurrent infections. Patient preferences regarding the frequency of dosing and route of administration should be weighed when selecting a specific TNFi.

In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab (new, PICO 58).

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab (new, PICO 59).

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib (new, PICO 60).

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib (new, PICO 61).

The use of secukinumab and ixekizumab in patients with active AS is supported by data from large placebo-controlled trials (see Supplementary Appendix 6, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). The panel recommended use of TNFi over secukinumab or ixekizumab based on greater experience with TNFi and familiarity with their long-term safety and toxicity. Similarly, the panel judged that TNFi, secukinumab, or ixekizumab should be used over tofacitinib, given the larger evidence base for TNFi, secukinumab, and ixekizumab. In patients with coexisting ulcerative colitis, if treatment with TNFi is not an option, tofacitinib should be considered over secukinumab or ixekizumab. Interleukin-17 (IL-17) inhibitors have not been shown to be efficacious in IBD, although tofacitinib is an approved treatment for ulcerative colitis (26,27).

In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib (new, PICO 8).

No studies have directly compared the risks and benefits of treatment alternatives in patients who have contraindications to treatment with TNFi. The panel favored treatment with secukinumab or ixekizumab over treatment with sulfasalazine or methotrexate based on a higher likelihood of benefit, but this recommendation was conditional on the specific contraindication. If the contraindication to TNFi use was the presence of congestive heart failure or demyelinating disease, secukinumab or ixekizumab was preferred, since these medications have not been shown to worsen these conditions. If the contraindication to TNFi use was tuberculosis, other chronic infection, or a high risk of recurrent infections, sulfasalazine was preferred over secukinumab, izekizumab, and tofacitinib. In these cases, efforts to mitigate the infections should be undertaken so that TNFi might safely be used. Treatment with rituximab, abatacept, ustekinumab, or IL-6 inhibitors is not recommended, even in patients with contraindications to TNFi, due to lack of effectiveness.

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary nonresponse to TNFi (new, PICO 10).

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary nonresponse to TNFi (new, PICO 10).

In adults with active AS despite treatment with the first TNFi used, we strongly recommend against switching to treatment with a biosimilar of the first TNFi (new, PICO 62).

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of switching to a new biologic (PICO 9).

Direct comparisons of treatment strategies for patients who do not have or sustain adequate responses to their first TNFi have not been reported, and the recommendations are based on the panel's consideration of indirect comparisons among the available treatment options (see Supplementary Appendix 6, at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Data from observational studies suggest that 25–40% of patients who switch from one TNFi to another will have a meaningful response (e.g.,

50% improvement in Bath AS Disease Activity Index) to the second TNFi (28–30). However, not all patients in these studies switched TNFi because of ineffectiveness.

The panel judged that treatment should differ for patients who had a primary nonresponse to TNFi and those with secondary nonresponse to TNFi. Switching to secukinumab or ixekizumab was recommended in most patients who had a primary nonresponse to the first TNFi, under the assumption that TNF was not the key inflammatory mediator in these patients. Continuing treatment with the first TNFi could be considered if additional time was believed important to assess the response fully, or if a higher dose or shorter dosing interval was thought to be beneficial.

In patients who relapse after an initial response (i.e., secondary nonresponse), the panel judged that treatment with a different TNFi held a reasonable prospect of benefit and should be used in most patients, rather than immediately switching to a different class of biologics. Although ixekizumab is efficacious among TNFi nonresponders, trials have not directly compared responses to ixekizumab (or secukinumab) to responses to a second TNFi in patients with a secondary nonresponse to the first TNFi (11). Given that options for biologics are limited, treatment with a second TNFi was recommended in these patients.

In cases of nonresponse (primary or secondary), the panel recommended against switching to the biosimilar of the first TNFi (e.g., switching from originator infliximab to infliximab-dyyb), as the clinical response would not be expected to be different. The panel also recommended against the addition of sulfasalazine or methotrexate to TNFi in cases of nonresponse to TNFi, judging any benefit would likely be marginal. The addition of sulfasalazine could be considered in the rare patient whose axial symptoms are well-controlled with TNFi but who has active peripheral arthritis.

In adults with either active or stable AS on treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate (new, PICO 64).

In rheumatoid arthritis, the likelihood of TNFi discontinuation is lower among patients who receive co-treatment with methotrexate, perhaps by reducing the development of antidrug antibodies (31). In AS, it is less clear whether the duration of TNFi use, and by inference their effectiveness, is similarly prolonged (32). Data from observational studies are conflicting, although some studies, primarily of infliximab, showed longer TNFi treatment when methotrexate was co-administered (see Supplementary Appendix 6 at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Clinical responses were not greater among patients who received co-treatment with methotrexate. In the absence of convincing evidence of benefit, and due to greater burden for patients, the panel recommended against routine co-administration of methotrexate with TNFi, although its use could be considered in patients treated with infliximab.

B. Recommendations for the treatment of patients with stable AS

In adults with stable AS, we conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs (PICO 1).

This recommendation applies to patients whose AS has been stable while not receiving any pharmacologic treatment. In this group, the panel considered that the potential toxicities of continuous NSAID treatment outweighed the uncertain benefit of less radiographic progression. On-demand treatment should be considered for short-term symptom recurrences (flares).

In adults with stable AS receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone over continuing both medications (PICO 11).

In adults with stable AS receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing both medications (PICO 12).

No new studies have directly compared outcomes between patients who continued combination treatment and those who discontinued either NSAIDs or a conventional synthetic antirheumatic drug (csARD). The NSAID-sparing potential of etanercept was demonstrated in a recent trial (33). The panel judged these recommendations primarily based on symptom control, rather than on any potential effect of combination therapy on future spinal fusion. In stable patients, a trial of withdrawing either the NSAIDs or the csARD should be considered, due to the likelihood of greater toxicity with the long-term use of more than one medication. However, on-demand NSAID treatment for control of intermittent symptoms is recommended for patients with good responses to previous courses of NSAIDs.

In adults with stable AS receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic (new, PICO 66).

In adults with stable AS receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach (new, PICO 65).

Data from several observational studies suggest that discontinuation of TNFi after achieving either remission or low disease activity results in relapses in 60–74% of patients, occasionally within a few weeks to months from discontinuation (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Although the data only concerned TNFi discontinuation, the panel judged that a similar recommendation would also apply to other biologics. In general, treatment with a biologic should be planned to be

continued long-term, barring toxicities. Discontinuation might be considered in patients in sustained remission (i.e., several years), with the anticipation that only one-third of patients would not experience relapse. Patient preferences should help guide this decision.

Tapering of TNFi could entail a change in either the dose or frequency of administration. Two controlled unblinded trials of tapering etanercept to 25 mg weekly versus maintaining the dose at 50 mg weekly in patients with stable AS showed that remission or partial remission was somewhat less likely among those in whom etanercept was tapered (34,35). In small observational studies, 53–70% of patients were still receiving their reduced dose at 2 years, but there is little evidence regarding maintenance of long-term remission after tapering of TNFi (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Therefore, the panel recommended against tapering of biologics as a standard approach. One condition in which tapering could be considered would be in patients with prolonged stable AS, if the patient and provider engage in shared decision-making.

In adults with stable AS receiving an originator TNFi, we strongly recommend continuing treatment with the originator TNFi over mandated switching to its biosimilar (new, PICO 63).

While the efficacy of originator and biosimilar TNFi is comparable, and although either could be chosen to initiate new courses of TNFi treatment, it was the opinion of the panel to recommend against mandated switching to a biosimilar during the course of treatment, in the absence of evidence of interchangability. Medication changes can increase the risk of destabilizing a patient's condition, and the panel judged that additional data were needed to understand the frequency of potential problems and concerns associated with switching patients who were stable on an originator TNFi to its biosimilar. Given these concerns, the panel judged that there should be a compelling rationale for switching medications, particularly in light of the marginal cost savings apparent for US patients (36).

C. Recommendations for adults with AS-related comorbidities

In adults with AS and recurrent uveitis, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics (PICO 29).

Evidence for this recommendation is limited to indirect comparisons of the rates of acute uveitis episodes in clinical trials or observational studies, rather than from direct comparisons (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Many reports showed overall rates of uveitis without separately reporting recurrences as opposed to incident episodes (37). The rates were generally lower for adalimumab and infliximab compared to etanercept. For example, a large observational study demonstrated rates of uveitis (per 100 patient-years) in patients receiving adalimumab, infliximab, and etanercept of 13.6, 27.5, and 60.3, respectively, compared to pretreatment rates of 36.8, 45.5, and 41.6, respectively (38). Adalimumab or infliximab are preferred over etanercept for the treatment of AS in patients with recurrent uveitis. Certolizumab or golimumab may also be considered, although supporting data are less substantial (39,40). Data from clinical trials suggest that rates of uveitis flares were not different between patients with AS treated with secukinumab and those treated with placebo, but more evidence is needed. Secukinumab was not efficacious in the treatment of panuveitis or posterior uveitis (41). Rates of uveitis flares among patients treated with ixekizumab have not been well-defined.

In adults with AS and IBD, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics (PICO 32).

This recommendation was based on limited indirect evidence on the risks of flares or new onset of IBD among patients with AS during treatment with biologics, and the much larger literature on the treatment of IBD in general. Patients with AS treated with infliximab or adalimumab have lower risks of IBD exacerbations than those treated with etanercept (see Supplementary Appendix 6, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Infliximab, adalimumab, and certolizumab are approved for the treatment of Crohn's disease, and infliximab, adalimumab, and golimumab are approved for the treatment of ulcerative colitis, while etanercept is not approved for either condition (42,43). This evidence is the basis for the recommendation favoring TNFi monoclonal antibody use in patients with AS and coexisting IBD. The choice of the particular TNFi monoclonal antibody should be made in consultation with the patient's gastroenterologist. Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease (44–46). Increased risks of IBD exacerbation appear to also occur with ixekizumab (47).

D. Recommendations for the treatment of patients with either active or stable nonradiographic axial spondyloarthritis

Parallel questions on pharmacologic treatment were investigated for patients with nonradiographic axial SpA. There were no relevant published data for 19 questions. There was high-quality evidence only for the use of TNFi in nonradiographic axial SpA, which was examined in several clinical trials. Low-quality or very low-quality evidence from single studies suggested no differences in outcomes among different TNFi in nonradiographic axial SpA, high likelihood of relapse following discontinuation of TNFi, and no association between co-treatment with nonbiologics and TNFi persistence (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract).

Therefore, the recommendations for nonradiographic axial SpA were largely extrapolated from evidence in AS (Table 3). The recommendations were identical in both patient groups with 1 notable exception: treatment with secukinumab or ixekizumab was strongly recommended over no treatment with secukinumab or ixekizumab in patients with AS, while use of these medications was conditionally recommended in patients with nonradiographic axial SPA, because trials in nonradiographic axial SPA have not been reported. Evidence on tofacitinib in nonradiographic axial SpA has not been reported.

E. Disease activity assessment and imaging

In adults with active AS, we conditionally recommend against using the treat-to-target strategy, which aims at a target of an Ankylosing Spondylitis Disease Activity Score <1.3 (or 2.1), over a treatment strategy based on physician assessment (new, PICO 67).

The concept of treat-to-target strategies is well-founded in chronic disease management for conditions that have an accurate measure of disease activity (often one that is asymptomatic, as in blood pressure or glycosylated hemoglobin), a tight link between this disease activity measure and future health outcomes, and evidence that maintaining a particular target in the disease activity measure is closely associated with better long-term health (48). The treat-to-target approach in AS is indirectly supported by associations between levels of AS activity and future radiographic progression but lacks robust direct evidence. Because adoption of this strategy would place additional burdens on patients and providers, the panel judged that more convincing evidence of benefit should be present before endorsing this change in practice. There was also concern that focus on a specific target could lead to rapid cycling through all currently available treatments in some patients. As reflected in the 2015 guidelines, quantifying disease activity is important to help guide treatment decisions.

In adults with AS of unclear activity while receiving a biologic, we conditionally recommend obtaining a spinal or pelvis MRI to assess activity (new, PICO 68).

In adults with nonradiographic axial SpA of unclear activity while receiving a biologic, we conditionally recommend obtaining a pelvis MRI to assess activity (new, PICO 81).

Because physical and laboratory measures are often normal despite active axial SpA, and because symptoms may be nonspecific, it may be difficult to know whether a patient is experiencing inflammation that warrants a change in treatment. Limited evidence suggests that knowledge of MRI findings in the spine and sacroiliac joints may alter treatment recommendations. However, the degree of inflammatory change on MRI may not correlate with treatment responses, and the location of inflammation on MRI may not correlate with the location of pain (49) (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). The panel judged that MRI could provide useful information in cases where the level of disease activity was unclear and where this information would influence treatment decisions. For patients with nonradiographic axial SpA, the imaging should focus on the sacroiliac joints. In interpreting MRI results, it is important to keep in mind the range and frequency of abnormalities, including bone marrow edema lesions, that may occur in individuals without axial SpA and that may not represent inflammation due to axial SpA (50,51). MRI is not recommended in patients in whom disease activity is either clearly clinically active or clinically stable, or when the results of MRI would not be expected to change treatment.

In adults with stable AS, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity (new, PICO 69).

In adults with stable nonradiographic axial SpA, we conditionally recommend against obtaining a spine or pelvis MRI to confirm inactivity (new, PICO 82).

Because the clinical assessment of inflammation in axial SpA has many limitations, questions may arise about whether subclinical inflammation that could be detected by MRI is being "missed" by either the physical examination, symptoms, or laboratory studies. Given the lack of evidence that obtaining an MRI in stable patients improves clinical outcomes, the only moderate sensitivity and specificity of MRI-defined abnormalities for measurement of activity in axial SpA, the burden of testing, and concern for possible overtreatment, the panel recommended against obtaining an MRI in this setting. MRI could be considered in circumstances where the clinician and patient differ in their assessment of whether the disease is stable.

In adults with active or stable AS receiving any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach (new, PICO 70).

In adults with active or stable nonradiographic axial SpA on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach (new, PICO 83).

Spine radiographs are useful for the diagnosis of axial SpA, in evaluating the extent of spinal fusion, and for investigating new spinal pain in patients with established AS. In research studies, small changes in the extent of spine damage can be detected in 20–35% of patients with AS over a 2-year interval (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). There is no evidence that monitoring serial changes in

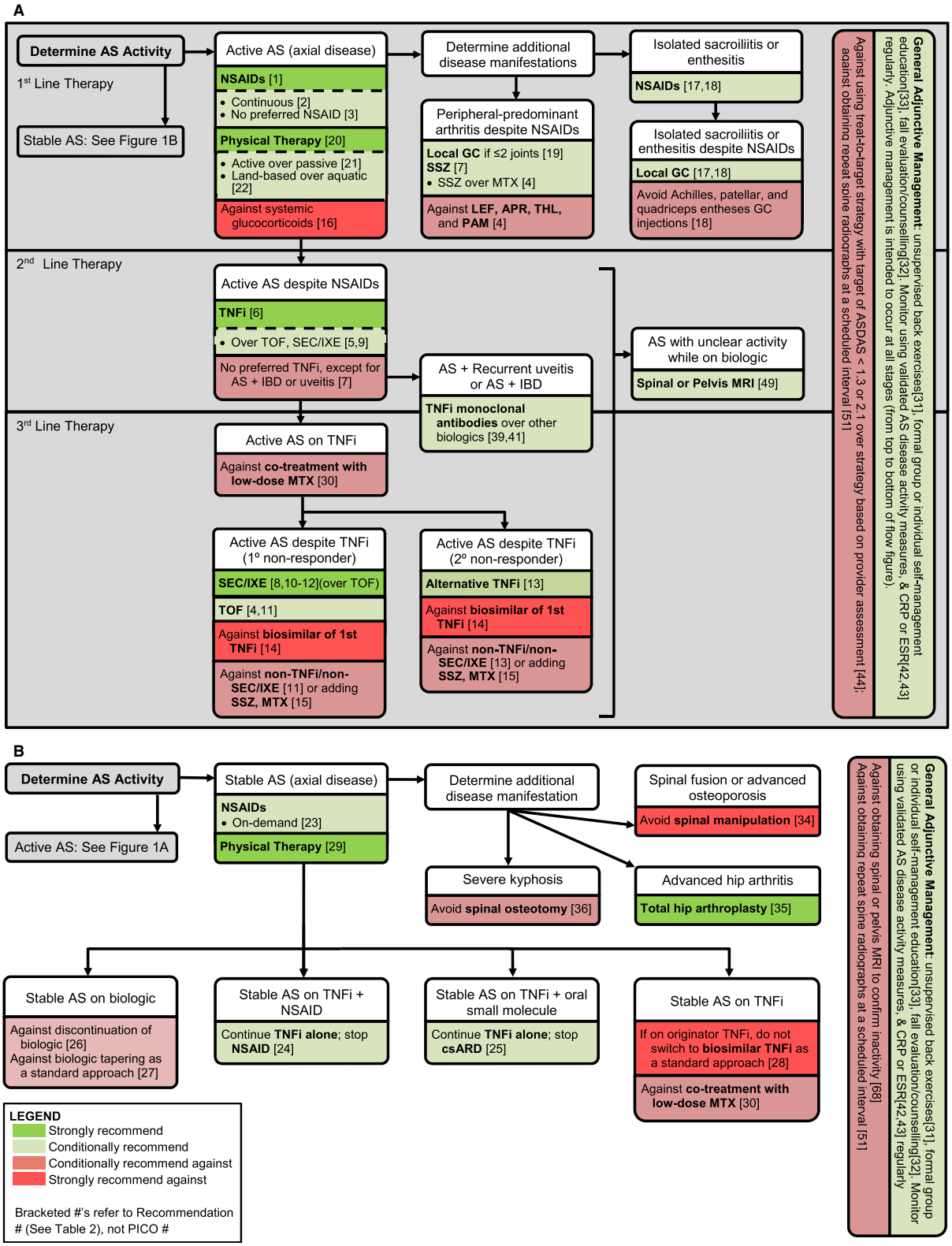
A
Determine AS Activity
1st Line Therapy
Stable AS: See Figure 1B
Active AS (axial disease)
NSAIDs [1]
• Continuous [2]
• No preferred NSAID [3]
Physical Therapy [20]
• Active over passive [21]
• Land-based over aquatic [22]
Against systemic glucocorticoids [16]
Determine additional disease manifestations
Peripheral-predominant arthritis despite NSAIDs
Local GC if ≤2 joints [19]
SSZ [7]
• SSZ over MTX [4]
Against LEF, APR, THL, and PAM [4]
Isolated sacroiliitis or enthesitis
NSAIDs [17,18]
Isolated sacroiliitis or enthesitis despite NSAIDs
Local GC [17,18]
Avoid Achilles, patellar, and quadriceps entheses GC injections [18]
2nd Line Therapy
Active AS despite NSAIDs
TNFi [6]
• Over TOF, SEC/IXE [5,9]
No preferred TNFi, except for AS + IBD or uveitis [7]
AS + Recurrent uveitis or AS + IBD
TNFi monoclonal antibodies over other biologics [39,41]
AS with unclear activity while on biologic
Spinal or Pelvis MRI [49]
3rd Line Therapy
Active AS on TNFi
Against co-treatment with low-dose MTX [30]
Active AS despite TNFi (1° non-responder)
SEC/IXE [8,10-12](over TOF)
TOF [4,11]
Against biosimilar of 1st TNFi [14]
Against non-TNFi/non-SEC/IXE [11] or adding SSZ, MTX [15]
Active AS despite TNFi (2° non-responder)
Alternative TNFi [13]
Against biosimilar of 1st TNFi [14]
Against non-TNFi/non-SEC/IXE [13] or adding SSZ, MTX [15]
General Adjunctive Management: unsupervised back exercises[31], formal group or individual self-management education[33], fall evaluation/counselling[32]. Monitor using validated AS disease activity measures, & CRP or ESR[42,43] regularly. Adjunctive management is intended to occur at all stages (from top to bottom of flow figure).
Against using treat-to-target strategy with target of ASDAS < 1.3 or 2.1 over strategy based on provider assessment [44]; against obtaining repeat spine radiographs at a scheduled interval [51]
B
Determine AS Activity
Active AS: See Figure 1A
Stable AS (axial disease)
NSAIDs
• On-demand [23]
Physical Therapy [29]
Determine additional disease manifestation
Spinal fusion or advanced osteoporosis
Avoid spinal manipulation [34]
Severe kyphosis
Avoid spinal osteotomy [36]
Advanced hip arthritis
Total hip arthroplasty [35]
Stable AS on biologic
Against discontinuation of biologic [26]
Against biologic tapering as a standard approach [27]
Stable AS on TNFi + NSAID
Continue TNFi alone; stop NSAID [24]
Stable AS on TNFi + oral small molecule
Continue TNFi alone; stop csARD [25]
Stable AS on TNFi
If on originator TNFi, do not switch to biosimilar TNFi as a standard approach [28]
Against co-treatment with low-dose MTX [30]
LEGEND
Strongly recommend
Conditionally recommend
Conditionally recommend against
Strongly recommend against
Bracketed #'s refer to Recommendation # (See Table 2), not PICO #
General Adjunctive Management: unsupervised back exercises[31], formal group or individual self-management education[33], fall evaluation/counselling[32]. Monitor using validated AS disease activity measures, & CRP or ESR[42,43] regularly
Against obtaining spinal or pelvis MRI to confirm inactivity [68]
Against obtaining repeat spine radiographs at a scheduled interval [51]

Figure 1. Summary of the main recommendations for the treatment of patients with **A,** active ankylosing spondylitis and **B,** stable ankylosing spondylitis. AS = ankylosing spondylitis; NSAIDs = nonsteroidal antiinflammatory drugs; GC = glucocorticoid; SSZ = sulfasalazine; MTX = methotrexate; LEF = leflunomide; APR = apremilast; THL = thalidomide; PAM = pamidronate; TNFi = tumor necrosis factor inhibitor; TOF = tofacitinib; SEC = secukinumab; IXE = ixekizumab; IBD = inflammatory bowel disease; csARD = conventional synthetic antirheumatic drugs; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein level; ASDAS = Ankylosing Spondylitis Disease Activity Score; MRI = magnetic resonance imaging; PICO = population, intervention, comparison, and outcomes.

spine radiographs at a regular interval leads to better patient outcomes, and data balancing a clinical benefit with the risk of radiation exposure are absent. Therefore, the panel recommended against repeating spine radiographs as a standard approach. In the absence of clinical indications, repeat spine radiographs could be considered on an ad hoc basis for counseling patients on the progression of their disease, which may help in career and life planning.

F. Summary of recommendations

Figure 1 presents a diagram of the main treatment recommendations for active and stable AS, integrating the new recommendations with the 2015 recommendations that were not updated in this review.

DISCUSSION

This update was primarily motivated by the availability of new treatment options, notably secukinumab, ixekizumab, tofacitinib, and TNFi biosimilars, for patients with axial SpA. Providers and patients have questions on where these new medications fit in the pharmacologic strategy, and how originator TNFi, sulfasalazine, and NSAIDs should be used given these new options. Based on the current evidence and the considerations of the panel, NSAIDs and TNFi remain the primary classes of medications for the treatment of AS and nonradiographic axial SpA. Secukinumab or ixekizumab is recommended for patients with active disease who have heart failure or demyelinating disease as a contraindication to TNFi, and in primary nonresponders to TNFi. Secukinumab and ixekizumab are not recommended in patients with IBD or recurrent uveitis, as TNFi monoclonal antibodies are better options. Tofacitinib is a potential second-line option for patients with contraindications to TNFi other than infections. Recommendations regarding tofacitinib may change pending the results of larger clinical trials.

Several of the 2015 recommendations were modified in this update. The current recommendation is conditionally in favor of use of sulfasalazine in limited clinical circumstances, whereas the 2015 recommendations had this as an exception to the general recommendation against the use of conventional synthetic antirheumatic drugs. In the 2015 recommendations, sulfasalazine and pamidronate were suggested as alternatives for the treatment of patients with active disease and contraindications to TNFi, while the current recommendations suggest use of secukinumab or ixekizumab in most of these cases (except patients with high risk of infections). In cases of failure of TNFi, the 2015 guidelines included a conditional recommendation for a trial of a second TNFi and against use of a non-TNFi biologic, whereas the current guidelines differentiate treatment recommendations based on whether there was primary or secondary nonresponse to the TNFi. For the treatment of patients with recurrent uveitis, the previous guidelines specified conditional use of infliximab or adalimumab, while the update broadened this recommendation to include TNFi monoclonal antibodies generally. Similarly, for patients with coexisting IBD, the update includes a conditional recommendation for TNFi monoclonal antibodies over other biologics, rather than over only etanercept. Finally, the recommendation for use of TNFi in patients with active nonradiographic axial SpA was changed from conditional to strong.

New questions on the treatment of patients with stable disease were addressed in this update. Discontinuation of biologics is not recommended due to the likelihood for symptom recurrence. If tapering is considered, patients should be counseled regarding the potential for increased disease activity. Co-treatment with low-dose methotrexate is not generally recommended, but ongoing studies will shed further light on this question. Switching to a biosimilar during the course of treatment with TNFi is also not recommended, echoing the concerns previously expressed by the ACR (52).

Imaging remains a central tool in the diagnosis of axial SpA, but its role in monitoring patients is less well-defined. Spine and/or pelvis MRI could aid in the evaluation of patients in whom the degree of active inflammation is uncertain, and especially in those for whom the findings would change management. MRI is not recommended to seek subclinical inflammation in patients with stable disease (as defined in Table 1). However, MRI could be considered in circumstances where it may inform shared decision-making. We recommend against obtaining spine radiographs on scheduled intervals to monitor progression. This practice entails radiation exposure and would not alter treatment in most cases.

We used the GRADE method to develop these treatment recommendations in a way that was transparent, systematic, and explicit, and that was informed by the medical evidence as well as patient preferences. The major limitation of these guidelines is the very low quality of evidence for many recommendations, which necessitated reliance on the clinical expertise of the panel. For nonradiographic axial SpA, most recommendations were based on extrapolation of results from studies in AS. We tried to identify the most common and consequential treatment questions, so that the recommendations would be useful in guiding clinical decision-making. The low quality of evidence for many questions is an indication that research has not yet tackled many of the most important treatment questions. As more treatment options become available, this problem will grow. Importantly, failure to recommend a particular medication does not imply that it is contraindicated. Key evidence gaps include the comparative effectiveness and safety of different biologics, the optimal sequencing of treatments, and the role of NSAIDs.

This update addressed only a subset of treatment questions. The 2015 recommendations that were not reexamined are to be considered extant. Recommendations are meant to describe the approach to treatment of the typical patient and cannot anticipate all possible clinical scenarios. Application of these recommendations must be individualized, and requires

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SPECIAL ARTICLE

2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the health care provider in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To develop an evidence-based guideline for the pharmacologic and nonpharmacologic treatment of psoriatic arthritis (PsA), as a collaboration between the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF).

Methods. We identified critical outcomes in PsA and clinically relevant PICO (population/intervention/comparator/outcomes) questions. A Literature Review Team performed a systematic literature review to summarize evidence supporting the benefits and harms of available pharmacologic and nonpharmacologic therapies for PsA. GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to rate the quality of the evidence. A voting panel, including rheumatologists, dermatologists, other health professionals, and patients, achieved consensus on the direction and the strength of the recommendations.

Results. The guideline covers the management of active PsA in patients who are treatment-naive and those who continue to have active PsA despite treatment, and addresses the use of oral small molecules, tumor necrosis factor inhibitors, interleukin-12/23 inhibitors (IL-12/23i), IL-17 inhibitors, CTLA4-Ig (abatacept), and a JAK inhibitor (tofacitinib). We also developed recommendations for psoriatic spondylitis, predominant enthesitis, and treatment in the presence of concomitant inflammatory bowel disease, diabetes, or serious infections. We formulated recommendations for a treat-to-target strategy, vaccinations, and nonpharmacologic therapies. Six percent of the recommendations were strong and 94% conditional, indicating the importance of active discussion between the health care provider and the patient to choose the optimal treatment.

Conclusion. The 2018 ACR/NPF PsA guideline serves as a tool for health care providers and patients in the selection of appropriate therapy in common clinical scenarios. Best treatment decisions consider each individual patient situation. The guideline is not meant to be proscriptive and should not be used to limit treatment options for patients with PsA.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, manifesting most commonly with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Nail lesions, including pitting and onycholysis, occur in ~80–90% of patients with PsA. The incidence of PsA is ~6 per 100,000 per year, and the prevalence is ~1–2 per 1,000 in the general population (1). The annual incidence of PsA in patients with psoriasis is 2.7% (2), and the reported prevalence of PsA among patients with psoriasis has varied between 6% and 41% (1). In the majority of patients the skin symptoms develop first, followed by the arthritis; however, in some patients the skin and joint symptoms present at the same time, and in 10–15% the arthritis presents first (2).

PsA affects men and women equally. The distribution of the peripheral arthritis varies from asymmetric oligoarthritis (involving ≤4 joints) to symmetric polyarthritis (involving ≥5 joints). Distal interphalangeal joints are commonly affected and, in some patients, are the only affected joints. Axial disease, when present, usually occurs together with peripheral arthritis. Some patients present with rapidly progressive and destructive PsA–arthritis mutilans. PsA is associated with an adverse impact on health-related quality of life (3–5) and high health care costs and utilization (6,7). Greater disease activity is associated with progressive joint damage and higher mortality (8–11). Early identification of PsA and early initiation of therapy are important for improving long-term outcomes (12).

Both nonpharmacologic and pharmacologic treatment can ameliorate PsA symptoms and can occasionally result

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in disease remission (Figure 1). Clinicians and patients can now choose from a wide variety of pharmacologic therapies, including symptomatic treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) and intraarticular injections, as well as immunomodulatory therapies.

The presentation of PsA is heterogeneous, and health care providers frequently face challenges when considering the various treatment options. Our objective was to develop evidence-based treatment recommendations for the management of active PsA in adults, using pharmacologic and nonpharmacologic therapies. These PsA treatment recommendations can help guide both clinicians and patients to arrive at optimal management decisions.

METHODS

Methodology overview. This guideline followed the American College of Rheumatology (ACR) guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (13–15) (www.gradeworkinggroup.org) to rate the quality of the available evidence and to develop the recommendations. ACR policy guided disclosures and the management of conflicts of interest. The full methods are presented in detail in Supplementary Appendix 1, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract.

This work involved 4 teams selected by the ACR Quality of Care Committee after reviewing individual and group volunteer applications in response to an open request for proposals announcement: 1) a Core Leadership Team, which supervised and coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, which completed the literature search and abstraction; 3) an Expert Panel, composed of patients, patient advocates, rheumatologists, dermatologists, 1 dermatologist-rheumatologist, and 1 rheumatology nurse practitioner, which developed the clinical questions (PICO [population/intervention/comparator/outcomes] questions) and decided on the scope of the guideline project; and 4) a Voting Panel, which included rheumatologists, 1 dermatologist, 1 dermatologist-rheumatologist, 1 rheumatology physician assistant, and 2 patients (1 of whom was also a physical therapist), who provided input from the patient perspective and voted on the recommendations. Additionally, a Patient Panel consisting of 9 adults with PsA reviewed the evidence and provided input on their values and preferences, which was reviewed before discussion of each section of PsA management (e.g., treatment-naive, treated, comorbidities), and was incorporated into discussions and formulation of recommendations. Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract) presents rosters of the team and panel members. In accordance with ACR policy, the principal investigator and the leader of the literature review team were free of conflicts, and within each team, >50% of the members were free of conflicts.

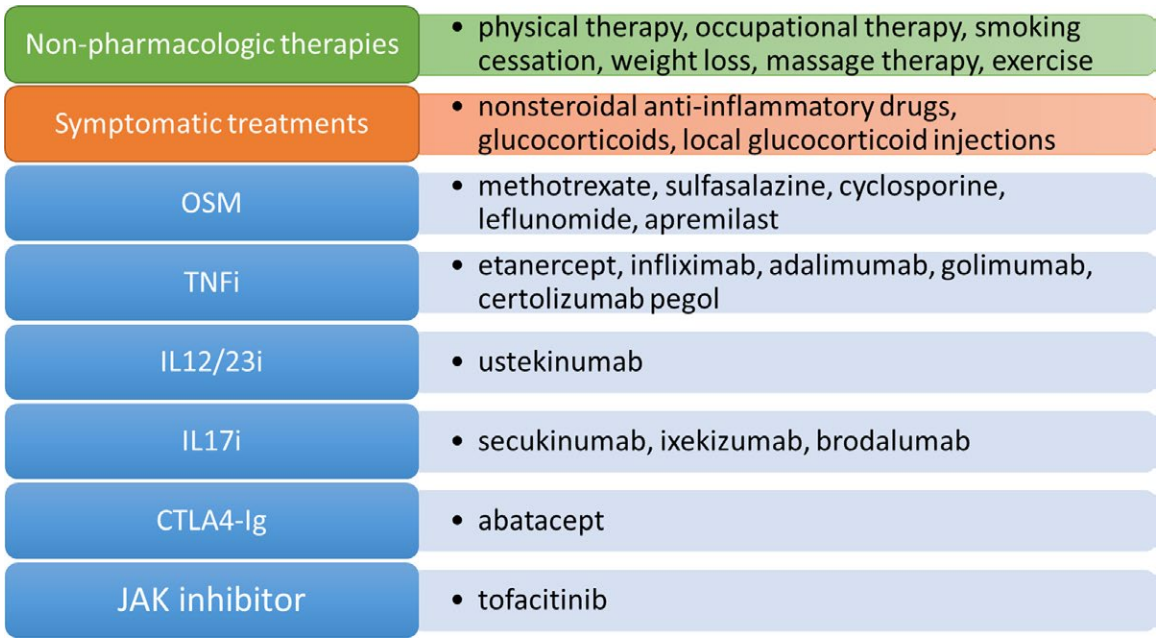

Figure 1. Pharmacologic, nonpharmacologic, and symptomatic therapies for psoriatic arthritis. Pharmacologic therapies are displayed in the blue boxes and include oral small molecules (OSMs), tumor necrosis factor inhibitor (TNFi) biologics, interleukin-17 inhibitor (IL-17i) biologics, an IL-12/23i biologic, CTLA4-immunoglobulin, and a JAK inhibitor. While there are numerous nonpharmacologic therapies available, 6 of these are addressed in this guideline. Symptomatic therapies include nonsteroidal antiinflammatory drugs, systemic glucocorticoids, and local glucocorticoid injections. Systemic glucocorticoids or local injections are not addressed in this guideline.

Framework for the PsA guideline development and scope of the guideline. Because there are numerous topics within PsA that could be addressed, at the beginning of the process the guideline panels made several decisions regarding the focus of this guideline and how to define aspects of the disease (e.g., active disease). At an initial scoping meeting, the Voting Panel and Expert Panel agreed that the project would include the management of patients with *active* PsA, defined as symptoms at an unacceptably bothersome level as reported by the patient and judged by the examining health care provider to be due to PsA based on the presence of at least 1 of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD). The health care provider may, in deciding if symptoms are due to active PsA, consider information beyond the core information from the history and physical examination, such as inflammation markers (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) and imaging results. At the scoping meeting, the panels decided that the guideline would address both pharmacologic and nonpharmacologic therapies for the treatment of PsA. We examined evidence regarding vaccinations, treatment in the presence of common comorbidities, and implementing a treat-to-target strategy.

In addressing pharmacologic therapies, we focused on immunomodulatory agents for long-term management rather than addressing acute symptom management (i.e., through intraarticular injections and the use of systemic glucocorticoids). Tofacitinib and ixekizumab were submitted for review and potential approval by the US Food and Drug Administration (FDA) at the time of formulation of this guideline (16,17) and for this reason, these drugs were addressed in the guideline. Both drugs have been approved for PsA since then (18,19). Tofacitinib is not included within the oral small molecules (OSM) category since its benefit/risk profile differs from that of the rest of the OSMs, especially with regard to risks (20–22), and consistent with its being considered separately in other treatment guidelines (23,24). Additionally, the panel addressed alternatives in patient subpopulations (e.g., patients with predominant enthesitis, axial disease, dactylitis, comorbidities), and greater versus lesser disease severity.

There are currently no widely agreed-upon definitions of disease severity in PsA or psoriasis. Thus, health care providers and patients should judge PsA and psoriasis severity on a case-by-case basis. For the purpose of these recommendations, severity includes not only the level of disease activity at a given time point, but also the presence or absence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of 1 or more of the following: a poor prognostic factor (erosive disease, dactylitis, elevated levels of inflammation markers such as ESR and CRP attributable to PsA), long-term damage that interferes with function (e.g., joint deformities), highly active disease that causes a major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease (Figure 2). In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) (25) score of ≥12 and a body surface area score of ≥10. However, because it is cumbersome, physicians seldom use the PASI in clinical practice. Examples of definitions of severe PsA and severe psoriasis are shown in Figure 2. Finally, because the National Psoriasis Foundation (NPF) and American Academy of Dermatology are concurrently developing psoriasis treatment guidelines, the treatment of skin psoriasis separately from the inflammatory arthritis was not included in the current ACR/NPF PsA guideline.

Systematic synthesis of the literature. Systematic searches of the published English-language literature included Ovid Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the beginning of each database through November 15, 2016 (Supplementary Appendix 3, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract); we conducted updated searches on May 2, 2017 and again on March 8, 2018. DistillerSR software (https://distillercer.com/products/distillersr-systematic-reviewsoftware/) (Supplementary Appendix 4; http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract) was used to facilitate duplicate screening of literature search results. Reviewers entered extracted data into RevMan software (http://tech.cochrane.org/revman), and evaluated the risk of bias in primary studies using the Cochrane risk of bias tool (http://handbook.cochrane.org/). We exported RevMan files into GRADEpro software to formulate a GRADE summary of findings table (Supplementary Appendix 5; http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract) for each PICO question (26). Additionally, a network meta-analysis was performed when sufficient studies were available. GRADE criteria provided the framework for judging the overall quality of evidence (13).

The panels chose the critical outcomes for all comparisons at the initial scoping; these included the American College of Rheumatology 20% response criteria (ACR20) (the primary outcome for most PsA clinical trials), the Health Assessment Questionnaire disability index (a measure of physical function), the PASI 75% response criteria (PASI75) (a measure of skin psoriasis improvement), and serious infections. Both the ACR20 and the PASI75 are accepted outcome measures specified by regulatory agencies, including the US FDA, for the approval of treatments for PsA (27). Serious infections are among the issues of greatest

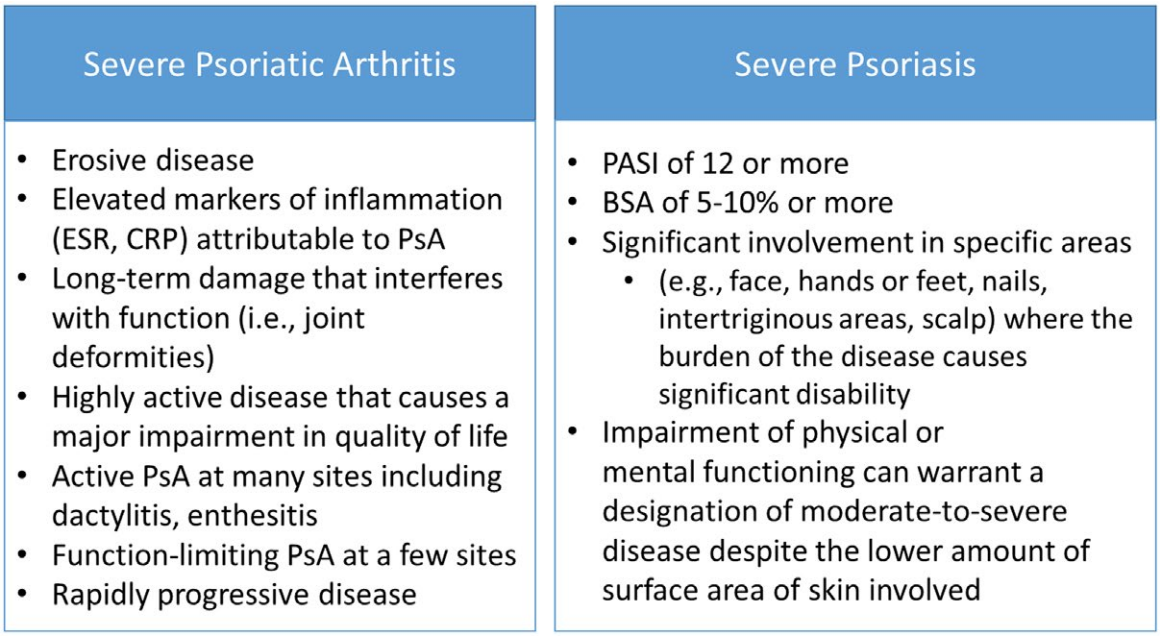
Severe Psoriatic Arthritis
• Erosive disease
• Elevated markers of inflammation (ESR, CRP) attributable to PsA
• Long-term damage that interferes with function (i.e., joint deformities)
• Highly active disease that causes a major impairment in quality of life
• Active PsA at many sites including dactylitis, enthesitis
• Function-limiting PsA at a few sites
• Rapidly progressive disease
Severe Psoriasis
• PASI of 12 or more
• BSA of 5-10% or more
• Significant involvement in specific areas
• (e.g., face, hands or feet, nails, intertriginous areas, scalp) where the burden of the disease causes significant disability
• Impairment of physical or mental functioning can warrant a designation of moderate-to-severe disease despite the lower amount of surface area of skin involved

Figure 2. Examples of "severe" psoriatic arthritis (PsA) and psoriasis. The guideline development group defined severe PsA and psoriasis as the presence of 1 or more of the items listed. This is not a formal definition. There have been many definitions of severe psoriasis used over time—the items here are adapted from the 2007 National Psoriasis Foundation expert consensus statement for moderate-to-severe psoriasis (68). In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score of ≥12 and a body surface area (BSA) score of ≥10 (25). ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

concern for patients and physicians when selecting among therapies. Other specific harms (e.g., liver toxicity with methotrexate [MTX]) were included as critical outcomes for individual comparisons. We included other outcomes, such as total infections (regardless of severity), when appropriate.

Moving from evidence to recommendations. GRADE methodology specifies that panels make recommendations based on the balance of benefits and harms, the quality of the evidence (i.e., confidence in effect estimates), and patients' values and preferences. Deciding on the balance between desirable and undesirable outcomes requires estimating the relative value patients place on those outcomes. When the literature provided very limited guidance, the experience of the Voting Panel members (including physicians, a rheumatology physician assistant, and the 2 patients present) in managing the relevant cases and issues became an important source of evidence. Values and preferences, crucial to all recommendations, derived from input from the members of the Patient Panel were particularly salient in such situations. GRADE methodology allows the panels the possibility of not coming to a decision, and a summary of the discussion is noted in such cases. However, during the development of this guideline, the Voting Panel came to a conclusion in each case scenario, and such a situation did not arise.

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. Recommendations required a 70% level of agreement, as used previously in other similar processes (28) and in the previous ACR guidelines (23,29,30); if 70% agreement was not achieved during an initial vote, the panel members held additional discussions before revoting. For all conditional recommendations, a written explanation is provided, describing the reasons for the decision and conditions under which the alternative choice may be preferable.

Moving from recommendations to practice. These recommendations are designed to help health care providers work with patients in selecting therapies. The presence or absence of concomitantly occurring conditions, such as IBD, uveitis, diabetes, and serious infections, and the knowledge of previous therapies, influence decisions regarding optimal management. In the context of PsA, the physical examination, which is also required for selecting therapy, includes assessment of the peripheral joints (including for dactylitis), the entheses, the spine, the skin, and the nails. Health care providers and patients must take into consideration all active disease domains, comorbidities, and the patient's functional status in choosing the optimal therapy for an individual at a given point in time.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations

1. A *strong recommendation* means that the panel was *confident* that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion of clinicians/patients not wanting to follow the recommendation. We use the phrase "*should use*" or "*should be used*" for strong recommendations.
2. A *conditional recommendation* means that the panel believed the desirable effects of following the recommendation *probably* outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but a small proportion of clinicians/patients may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. We use the phrase "*is recommended over*" or "*is/would be recommended*" for conditional recommendations. We specify conditions under which the less preferred drug may be used by using the phrase "*may be used*" or "*may consider*" or "*Y (less preferred drug) may be used instead of X (preferred drug)*" or "*may consider Y instead of X (preferred drug)*" for conditional recommendations.
3. Conditional recommendations were usually based on low- to very-low-quality evidence (in rare instances, moderate-quality evidence). Strong recommendations were typically based on moderate- or high-quality evidence.
4. For each recommendation, Supplementary Appendix 5 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract) provides details regarding the PICO questions and the GRADE evidence tables.
5. In each case, the Voting Panel's recommendation was based on a judgment of the most likely net benefit, i.e.,1) more benefit with the medication conditionally recommended with no difference in harms between the medications being compared (e.g., choosing a TNFi over OSMs in treatment-naive patients) or 2) less harm with the medication conditionally recommended and no difference in benefit (e.g., choosing abatacept over a TNFi in patients at risk of or with a history of previous infections, or preferring a different OSM over MTX in patients with PsA and diabetes due to an increased risk of liver toxicity in this subpopulation).
6. This is an evidence-based guideline, in that we explicitly use the best evidence available and present that in a transparent manner for the clinician reader/user (31,32). In some instances, this includes a randomized trial directly comparing the interventions under consideration. In other cases, in the absence of any published evidence, the best evidence comes from the collective experience of the Voting Panel and patient panel members, which in the GRADE system is rated as "very-low-quality" evidence.

Recommendations for pharmacologic interventions

Active PsA in treatment-naive patients (Table 1 and Figure 3). *All recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low-quality evidence.*

In treatment-naive patients with active PsA, a TNFi biologic agent is recommended over an OSM as a first-line option (Table 1). OSMs may be used instead of a TNFi biologic in patients without severe PsA and without severe psoriasis (as defined in Methods and Figure 2; final determination of severity to be made by the patient and the health care provider), those who prefer an oral drug instead of parenteral therapy, or those with contraindications to TNFi treatment, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.

For treatment-naive patients with active PsA, the use of a TNFi biologic or OSM is recommended over an interleukin-17 inhibitor (IL-17i) or IL-12/23i biologic. An IL-17i or IL-12/23i biologic may be used instead of TNFi biologics in patients with severe psoriasis or contraindications to TNFi biologics, and may be used instead of OSMs in patients with severe psoriasis or severe PsA. MTX is recommended over NSAIDs in treatment-naive patients with active PsA. NSAIDs may be used instead of MTX after consideration of possible contraindications and side effect profile in patients without evidence of severe PsA or severe psoriasis and in those at risk for liver toxicity (Table 1 and Figure 3). An IL-17i biologic is recommended over an IL-12/23i biologic. IL-12/23i biologics may be used in patients who have concomitant IBD or who desire less frequent drug administration.

Active PsA despite treatment with an OSM (Table 2 and Figure 4). *All recommendations for patients with active PsA despite treatment with an OSM are conditional based on mostly low- to very-low-quality evidence and, in a few instances, moderate-quality evidence.*

In patients with active PsA despite OSM therapy, switching to a TNFi, an IL-17i, or an IL-12/23i biologic is recommended over switching to a different OSM (Table 2 and Figure 4). A different OSM may be used rather than a TNFi, IL-17i, or IL-12/23i in patients who prefer an oral medication or those without evidence of severe PsA or severe psoriasis; a differ-

Table 1. Recommendations for the initial treatment of patients with active psoriatic arthritis who are OSM- and other treatment–naive (PICOs 9–15)*

	Level of evidence (evidence [refs.] reviewed)†
In OSM- and other treatment–naive patients with active PsA,	
1. **Treat with a TNFi biologic over an OSM** (MTX, SSZ, LEF, CSA, or APR) (PICO 10a–e) **Conditional recommendation** based on low-quality evidence; may consider an OSM if the patient does not have severe PsA,‡ does not have severe psoriasis,§ prefers oral therapy, has concern over starting a biologic as the first therapy, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (53–66)
2. **Treat with a TNFi biologic over an IL-17i biologic** (PICO 14) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i biologic if the patient has severe psoriasis or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
3. **Treat with a TNFi biologic over an IL-12/23i biologic** (PICO 13) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has severe psoriasis, prefers less frequent drug administration, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
4. **Treat with an OSM over an IL-17i biologic** (PICO 12) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i biologic if the patient has severe psoriasis and/or severe PsA.	Very low
5. **Treat with an OSM over an IL-12/23i biologic** (PICO 11) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD and/or severe psoriasis and/or severe PsA or prefers less frequent drug administration.	Very low
6. **Treat with MTX over NSAIDs** (PICO 9) **Conditional recommendation** based on very-low-quality evidence; may consider NSAIDs before starting MTX in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.	Very low (67)
7. **Treat with an IL-17i biologic over an IL-12/23i biologic** (PICO 15) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration.	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), cyclosporine (CSA), or apremilast (APR) and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and other treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi,) interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.

† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.

§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

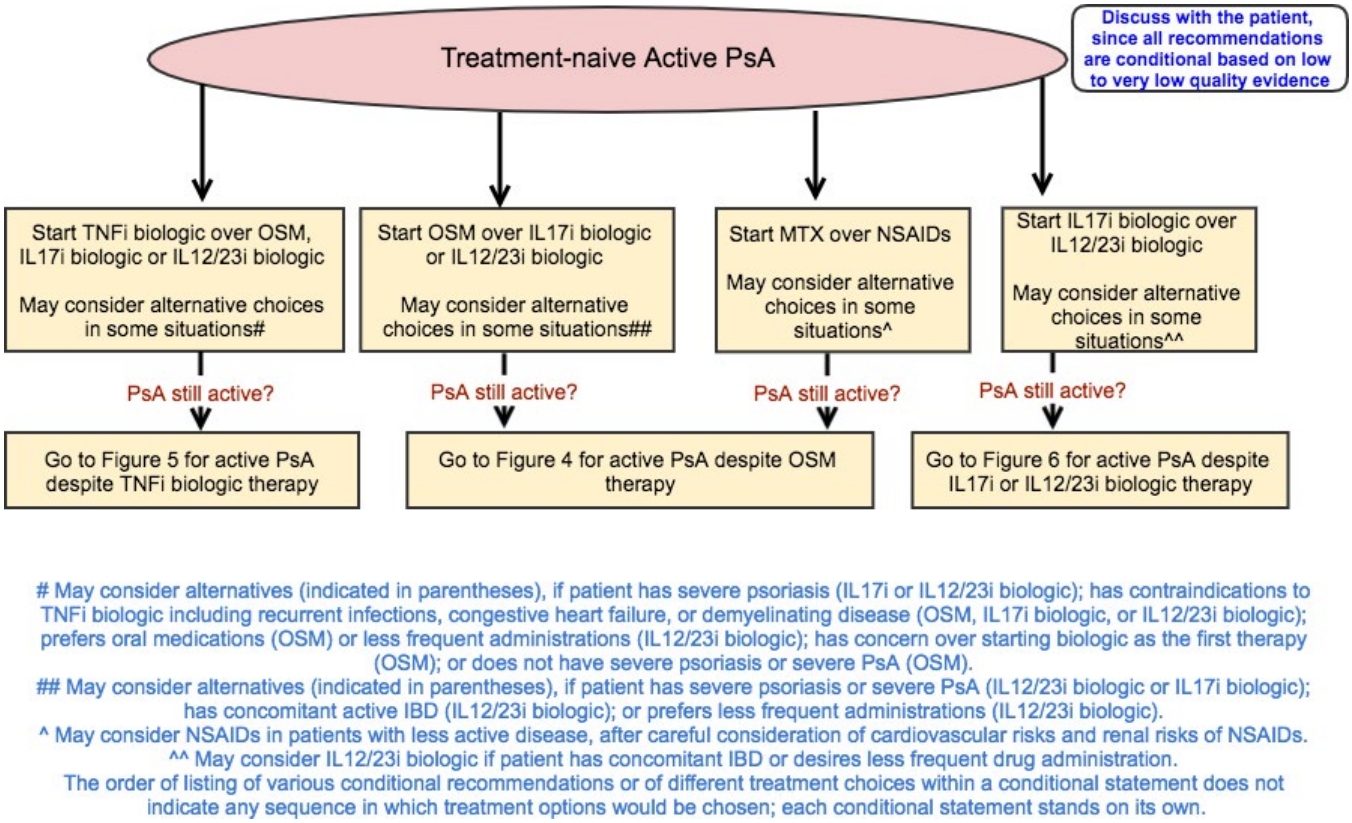
Treatment-naive Active PsA
Discuss with the patient, since all recommendations are conditional based on low to very low quality evidence
Start TNFi biologic over OSM, IL17i biologic or IL12/23i biologic
May consider alternative choices in some situations#
Start OSM over IL17i biologic or IL12/23i biologic
May consider alternative choices in some situations##
Start MTX over NSAIDs
May consider alternative choices in some situations^
Start IL17i biologic over IL12/23i biologic
May consider alternative choices in some situations^^
PsA still active?
PsA still active?
PsA still active?
PsA still active?
Go to Figure 5 for active PsA despite TNFi biologic therapy
Go to Figure 4 for active PsA despite OSM therapy
Go to Figure 6 for active PsA despite IL17i or IL12/23i biologic therapy
May consider alternatives (indicated in parentheses), if patient has severe psoriasis (IL17i or IL12/23i biologic); has contraindications to TNFi biologic including recurrent infections, congestive heart failure, or demyelinating disease (OSM, IL17i biologic, or IL12/23i biologic); prefers oral medications (OSM) or less frequent administrations (IL12/23i biologic); has concern over starting biologic as the first therapy (OSM); or does not have severe psoriasis or severe PsA (OSM).
May consider alternatives (indicated in parentheses), if patient has severe psoriasis or severe PsA (IL12/23i biologic or IL17i biologic); has concomitant active IBD (IL12/23i biologic); or prefers less frequent administrations (IL12/23i biologic).
^ May consider NSAIDs in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.
^^ May consider IL12/23i biologic if patient has concomitant IBD or desires less frequent drug administration.
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Figure 3. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) who are treatment-naive (no exposure to oral small molecules [OSMs] or other treatments). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 1 and the related section in the Results. This figure is derived from recommendations based on PICO (population/intervention/comparator/outcomes) questions that are based on the common clinical situations. Active PsA was defined as symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining health care provider to be due to PsA based on the presence of at least 1 of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD). TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor; MTX = methotrexate; NSAIDs = nonsteroidal antiinflammatory drugs.

ent OSM may be used rather than a TNFi in the presence of contraindications to TNFi biologics. A TNFi biologic is recommended over an IL-17i biologic, an IL-12/23i biologic, abatacept, or tofacitinib. An IL-17i biologic is recommended over an IL-12/23i biologic, abatacept, or tofacitinib. An IL-12/23i is recommended over abatacept or tofacitinib. In patients with contraindications to TNFi agents, an IL-12/23i, an IL-17i, abatacept, or tofacitinib may be used instead of a TNFi. In patients with severe psoriasis, an IL-12/23i or an IL-17i may be used instead of a TNFi. Tofacitinib may be used instead of a TNFi in patients preferring oral medication who do not have severe psoriasis.

Switching to another OSM is recommended over adding another OSM to the current treatment (except in the case of apremilast). Adding another OSM (except apremilast) to current treatment may be considered if the patient has exhibited partial response to the current OSM. Adding apremilast to the current OSM therapy is recommended over switching to apremilast monotherapy since most evidence for benefits of apremilast pertains to apremilast combination therapy. Switching to apremilast monotherapy may be considered instead of apremilast combination therapy if the patient has intolerable side effects with the current OSM.

Biologic monotherapy is recommended over biologic combination therapy with MTX (the most commonly used OSM in combination therapy). When switching to biologic monotherapy, stopping the OSM or tapering of the OSM are both reasonable options and depend on patient and health care provider

Table 2. Recommendations for treatment of patients with active psoriatic arthritis despite treatment with an OSM (PICOs 16–25; 67–69; 76–78)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA despite treatment with an OSM,	
1. **Switch to a TNFi biologic over a different OSM** (PICO 23) **Conditional recommendation** based on moderate-quality evidence; may consider switching to a different OSM if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, if the patient prefers an oral versus parenteral therapy, or in patients without evidence of severe PsA‡ or severe psoriasis.§	Moderate (62–66, 69–86)
2. **Switch to a TNFi biologic over an IL-17i biologic** (PICO 17) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-17i if the patient has severe psoriasis and/or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, and/or a family history of demyelinating disease such as multiple sclerosis.	Moderate (62–66, 72–78, 87–97)
3. **Switch to a TNFi biologic over an IL-12/23i biologic** (PICO 16) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-12/23i if the patient has severe psoriasis and/or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Moderate (62–66, 72–78, 97–102)
4. **Switch to a TNFi biologic over abatacept** (PICO 67) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (62–66, 72–78, 103, 104)
5. **Switch to a TNFi biologic over tofacitinib** (PICO 76) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers oral medication.	Low (62–66, 72–78, 105)
6. **Switch to an IL-17i over a different OSM** (PICO 25) **Conditional recommendation** based on low-quality evidence; may consider switching to a different OSM if the patient prefers an oral versus parenteral therapy or in patients without evidence of severe PsA or severe psoriasis.	Low (79–87, 89–95)
7. **Switch to an IL-17i biologic over an IL-12/23i biologic** (PICO 18) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration.	Moderate (87, 89–95, 98–100, 106, 107)
8. **Switch to an IL-17i biologic over abatacept** (PICO 69) **Conditional recommendation** based on low-quality evidence; may consider abatacept in patients with recurrent or serious infections.	Low (89–95, 103, 104)
9. **Switch to an IL-17i biologic over tofacitinib** (PICO 78) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or has a history of recurrent *Candida i*nfections.	Low (89–95, 105)
10. **Switch to an IL-12/23i biologic over a different OSM** (PICO 24) **Conditional recommendation** based on low-quality evidence; may consider switching to a different OSM if the patient prefers an oral versus parenteral therapy or in patients without evidence of severe PsA or severe psoriasis.	Low (79–86, 98–100)
11. **Switch to an IL-12/23i biologic over abatacept** (PICO 68) **Conditional recommendation** based on low-quality evidence; may consider abatacept in patients with recurrent or serious infections.	Low (98–100, 103, 104)

Table 2. *(Cont'd)*

	Level of evidence (evidence [refs.] reviewed)†
12. **Switch to an IL-12/23i biologic over tofacitinib** (PICO 77) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy.	Low (98–100, 105)
13. **Add apremilast to current OSM therapy over switching to apremilast** (PICO 22b) **Conditional recommendation** based on low-quality evidence; may consider switching to apremilast if the patient has intolerable side effects with the current OSM.	Low (83, 84, 108)
14. **Switch to another OSM (except apremilast) over adding another OSM (except apremilast) to current treatment** (PICO 22a) **Conditional recommendation** based on low-quality evidence; may consider adding another OSM (except apremilast) to current treatment if the patient has demonstrated partial response to the current OSM.	Low (83, 84, 108)
15. **Switch to a TNFi biologic monotherapy over MTX and a TNFi biologic combination therapy** (PICO 19) **Conditional recommendation** based on low-quality evidence; may consider MTX and TNFi biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, has concomitant uveitis (since uveitis may respond to MTX therapy), and if the current TNFi biologic is infliximab or adalimumab.	Low (109–111)
16. **Switch to an IL-17i biologic monotherapy over MTX and an IL-17i biologic combination therapy** (PICO 21) **Conditional recommendation** based on very-low-quality evidence; may consider MTX and an IL-17i biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy).	Very low
17. **Switch to an IL-12/23i biologic monotherapy over MTX and an IL-12/23i biologic combination therapy** (PICO 20) **Conditional recommendation** based on very-low-quality evidence; may consider MTX and an IL-12/23i biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy).	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor.

† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.

§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

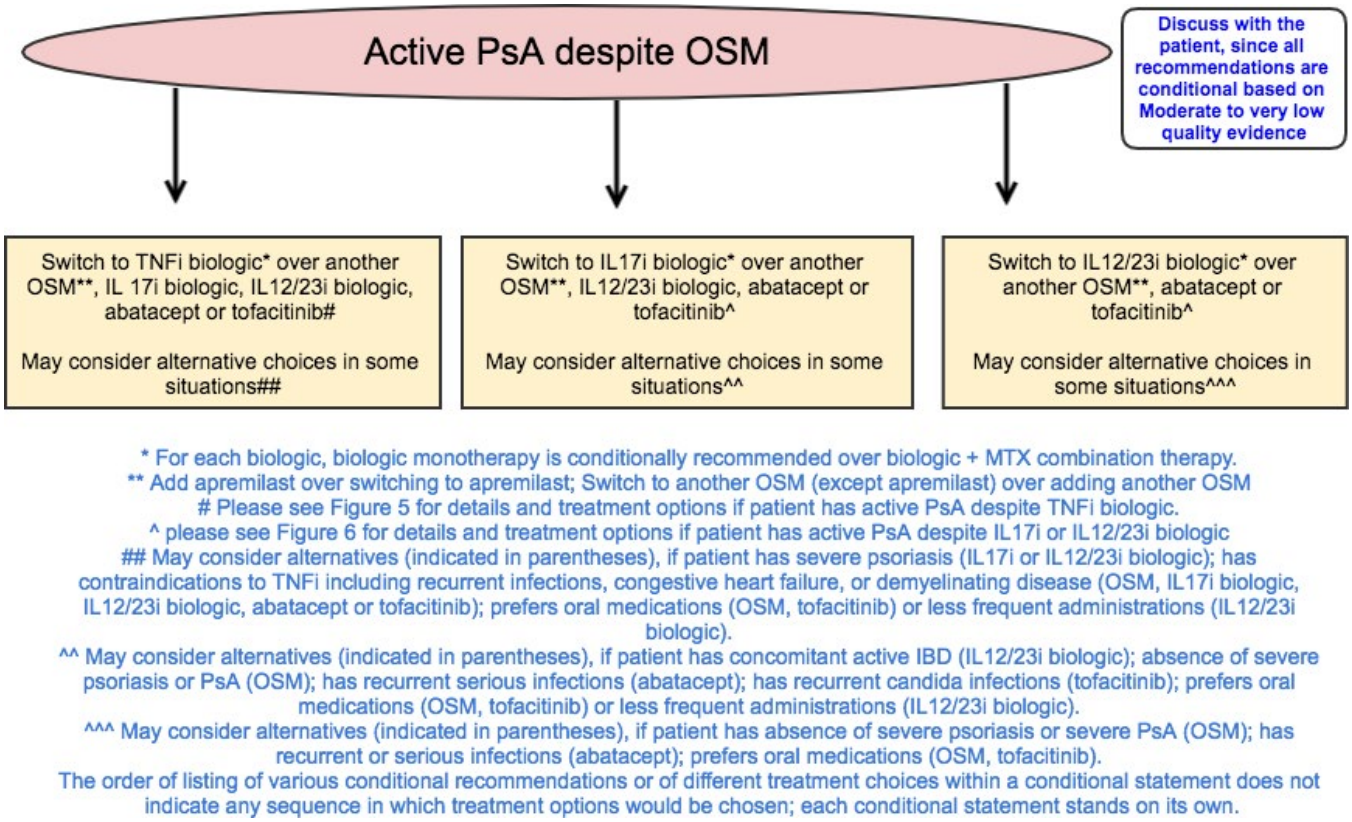
Active PsA despite OSM
Discuss with the patient, since all recommendations are conditional based on Moderate to very low quality evidence
Switch to TNFi biologic* over another OSM**, IL 17i biologic, IL12/23i biologic, abatacept or tofacitinib#
May consider alternative choices in some situations##
Switch to IL17i biologic* over another OSM**, IL12/23i biologic, abatacept or tofacitinib^
May consider alternative choices in some situations^^
Switch to IL12/23i biologic* over another OSM**, abatacept or tofacitinib^
May consider alternative choices in some situations^^^
* For each biologic, biologic monotherapy is conditionally recommended over biologic + MTX combination therapy.
** Add apremilast over switching to apremilast; Switch to another OSM (except apremilast) over adding another OSM
# Please see Figure 5 for details and treatment options if patient has active PsA despite TNFi biologic.
^ please see Figure 6 for details and treatment options if patient has active PsA despite IL17i or IL12/23i biologic
May consider alternatives (indicated in parentheses), if patient has severe psoriasis (IL17i or IL12/23i biologic); has contraindications to TNFi including recurrent infections, congestive heart failure, or demyelinating disease (OSM, IL17i biologic, IL12/23i biologic, abatacept or tofacitinib); prefers oral medications (OSM, tofacitinib) or less frequent administrations (IL12/23i biologic).
^^ May consider alternatives (indicated in parentheses), if patient has concomitant active IBD (IL12/23i biologic); absence of severe psoriasis or PsA (OSM); has recurrent serious infections (abatacept); has recurrent candida infections (tofacitinib); prefers oral medications (OSM, tofacitinib) or less frequent administrations (IL12/23i biologic).
^^^ May consider alternatives (indicated in parentheses), if patient has absence of severe psoriasis or severe PsA (OSM); has recurrent or serious infections (abatacept); prefers oral medications (OSM, tofacitinib).
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Figure 4. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with oral small molecules (OSMs). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 2 and the related section in the Results. TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor; MTX = methotrexate.

preferences. A biologic agent in combination with MTX may be used instead of biologic monotherapy if the patient has severe psoriasis, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy), or in patients receiving treatment with a monoclonal antibody TNFi biologic, especially infliximab and adalimumab, to potentially delay or prevent the formation of antidrug antibodies.

Active PsA despite treatment with a TNFi biologic agent as monotherapy or in combination therapy (Table 3 and Figure 5). *All recommendations for patients with active PsA despite TNFi biologic treatment are conditional based on low- to very-low-quality evidence.*

In patients with active PsA despite treatment with TNFi biologic monotherapy, switching to a different TNFi biologic monotherapy is recommended over switching to IL-12/23i biologic, an IL-17i biologic, abatacept, or tofacitinib monotherapy or adding MTX to the current TNFi biologic (Table 3 and Figure 5). An IL-12/23i biologic, IL-17i biologic, abatacept, or tofacitinib may be used instead of a different TNFi biologic monotherapy in the case of a primary TNFi biologic failure or a serious adverse event due to the TNFi biologic. An IL-17i or IL-12/23i biologic may be used instead of a different TNFi biologic, particularly in the presence of severe psoriasis. Abatacept may be used instead of a TNFi biologic in patients with recurrent or serious infections in the absence of severe psoriasis, based on indirect evidence of fewer hospitalized infections with abatacept compared to TNFi biologics in a population with rheumatoid arthritis (33). Tofacitinib may be used instead of a TNFi biologic if oral therapy is preferred by the patient.

In patients with active PsA despite treatment with TNFi biologic monotherapy, an IL-17i biologic is recommended over an IL-12/23i biologic, abatacept, or tofacitinib, and an IL-12/23i biologic is recommended over abatacept or tofacitinib. An IL-12/23i biologic may be considered instead of an IL-17i biologic if the patient has IBD or desires less frequent drug administration. Abatacept may be considered instead of an IL-17i or IL-

Table 3. Recommendations for treatment of patients with active psoriatic arthritis despite treatment with a TNFi biologic, as monotherapy or in combination with MTX (PICOs 26–35; 70–75)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA despite treatment with a TNFi biologic monotherapy,	
1. **Switch to a different TNFi biologic over switching to an IL-17i biologic** (PICO 28) **Conditional recommendation** based on low-quality evidence; may consider an IL-17i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse event or severe psoriasis.‡	Low (72, 73, 90–93, 95)
2. **Switch to a different TNFi biologic over switching to an IL-12/23i biologic** (PICO 27) **Conditional recommendation** based on low-quality evidence; may consider an IL-12/23i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect or prefers less frequent drug administration.	Low (72, 73, 99, 100)
3. **Switch to a different TNFi biologic over switching to abatacept** (PICO 70) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient had a primary TNFi biologic efficacy failure or TNFi biologic–associated serious adverse effect.	Low (72, 73, 103, 104)
4. **Switch to a different TNFi biologic over switching to tofacitinib** (PICO 73) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect.	Low (62–66, 72–78, 105)
5. **Switch to a different TNFi biologic (with or without MTX) over adding MTX to the same TNFi biologic monotherapy** (PICO 26 and 26A) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX when patients have demonstrated partial response to the current TNFi biologic therapy, especially if the TNFi biologic is a monoclonal antibody.	Very low
6. **Switch to an IL-17i biologic over switching to an IL-12/23i biologic** (PICO 29) **Conditional recommendation** based on low-quality evidence; may consider an IL-12/23i if the patient has IBD or if the patient prefers less frequent drug administration.	Low (90–93, 95, 99, 100)
7. **Switch to an IL-17i biologic over abatacept** (PICO 72) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient prefers IV dosing or in patients with recurrent or serious infections.	Low (90–93, 95, 103, 104, 112)
8. **Switch to an IL-17i biologic over tofacitinib** (PICO 75) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or in patients with concomitant IBD or a history of recurrent *Candida* infections.	Low (90–93, 105)
9. **Switch to an IL-12/23i biologic over abatacept** (PICO 71) **Conditional recommendation** based on of low-quality evidence; may consider abatacept if the patient prefers IV dosing or in patients with recurrent or serious infections.	Low (99, 100, 103, 104)
10. **Switch to an IL-12/23i biologic over tofacitinib** (PICO 74) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy.	Low (98–100, 105)
11. **Switch to a different TNFi biologic monotherapy over switching to a different TNFi biologic and MTX combination therapy** (PICO 30) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a TNFi biologic and MTX combination therapy if the current TNFi biologic is infliximab.	Very low
12. **Switch to an IL-17i biologic monotherapy over switching to an IL-17i biologic and MTX combination therapy** (PICO 32) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic and MTX combination therapy in patients with concomitant uveitis, as uveitis may respond to MTX therapy.	Very low

Table 3. *(Cont'd)*

	Level of evidence (evidence [refs.] reviewed)†
13. **Switch to an IL-12/23i biologic monotherapy over switching to an IL-12/23i biologic and MTX combination therapy** (PICO 31) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-12/23i biologic and MTX combination therapy if the patient has severe psoriasis.	Very low
In adult patients with active PsA despite treatment with a TNFi biologic and MTX combination therapy,	
14. **Switch to a different TNFi biologic + MTX over switching to a different TNFi biologic monotherapy** (PICO 33) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different TNFi biologic monotherapy if the patient has demonstrated MTX-associated adverse events, prefers to receive fewer medications, or perceives MTX as a burden.	Very low
15. **Switch to an IL-17i biologic monotherapy over an IL-17i biologic and MTX combination therapy** (PICO 35) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic and MTX combination therapy if the patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL-17i biologic was discussed as potentially beneficial to allow the new therapy time to work.	Very low
16. **Switch to IL-12/23i biologic monotherapy over IL-12/23i biologic and MTX combination therapy** (PICO 34) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-12/23i biologic and MTX combination therapy if the patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL-12/23i biologic was discussed as potentially beneficial to allow the new therapy time to work.	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). TNFi = tumor necrosis factor inhibitor; MTX = methotrexate; IL-17i = interleukin-17 inhibitor; IV = intravenous.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

12/23i biologic in patients with recurrent or serious infections. Tofacitinib may be considered instead of an IL-17i biologic in patients who prefer oral therapy or have a history of recurrent or severe *Candida* infections. Tofacitinib may be considered instead of an IL-12/23i biologic in patients who prefer oral therapy. For each biologic (TNFi, IL-12/23i, or IL-17i), monotherapy is recommended over combination with MTX. Combination therapy with biologic and MTX may be used instead of biologic monotherapy in the presence of severe psoriasis, partial response to current MTX therapy, concomitant uveitis (since uveitis may respond to MTX therapy), and if the current TNFi biologic is infliximab or adalimumab (for immunogenicity prevention).

Under circumstances in which combination therapy with a TNFi biologic and MTX is used and active PsA persists, switching to a different TNFi with MTX is recommended over monotherapy with a different TNFi. Continuing MTX treatment during TNFi transition was seen as beneficial because TNFi biologics may have more sustained efficacy when used in combination with MTX, but evidence is limited (34). Monotherapy with a different TNFi biologic may be used if the patient has had MTX-associated adverse events, prefers to receive fewer medications, or perceives MTX treatment as a burden. IL-12/23i or IL-17i biologic monotherapy is recommended over either of these agents in combination with MTX. Combination therapy with an IL-17i or IL-12/23 biologic and MTX may be used instead of switching to biologic monotherapy

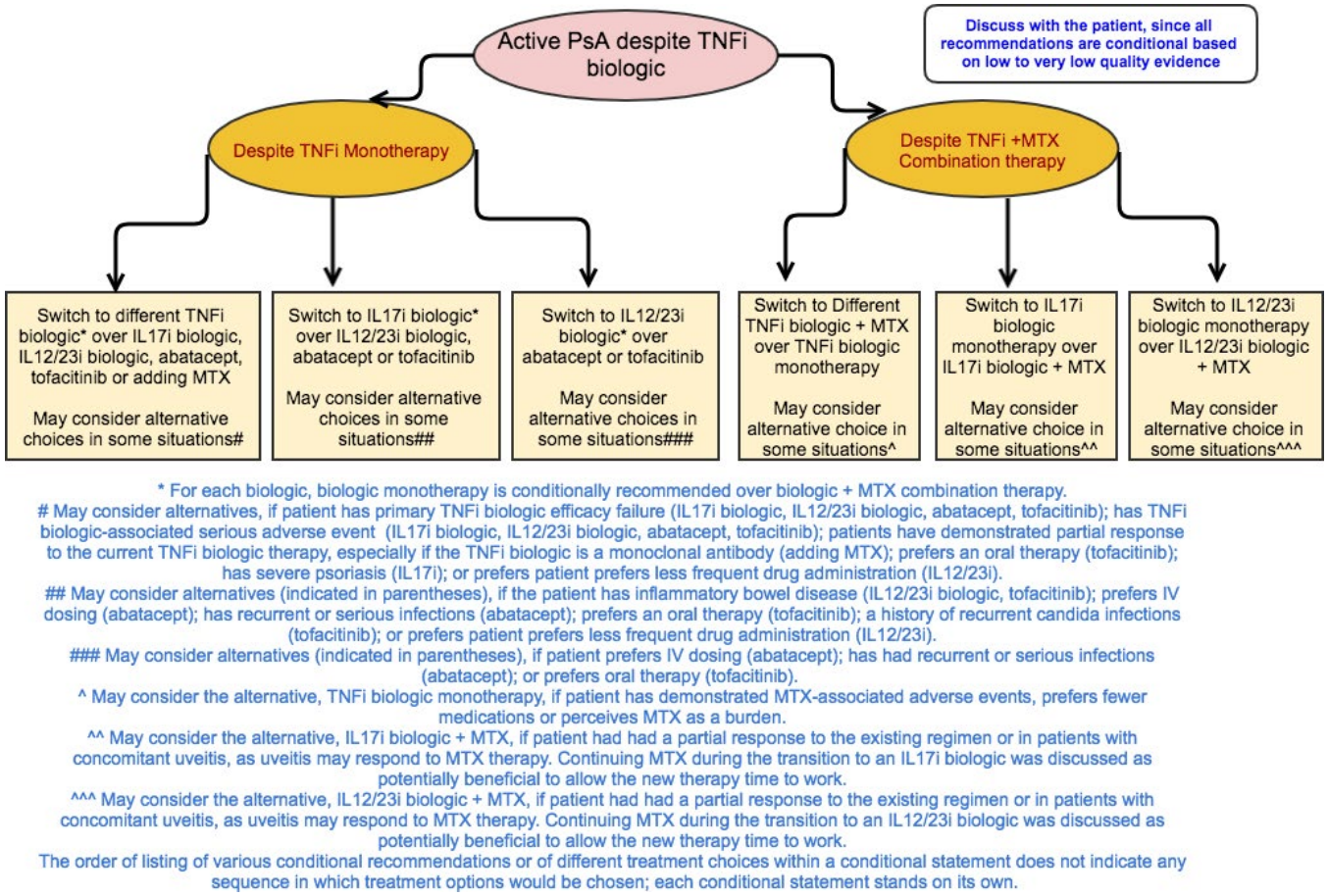
Active PsA despite TNFi biologic
Discuss with the patient, since all recommendations are conditional based on low to very low quality evidence
Despite TNFi Monotherapy
Despite TNFi +MTX Combination therapy
Switch to different TNFi biologic* over IL17i biologic, IL12/23i biologic, abatacept, tofacitinib or adding MTX
May consider alternative choices in some situations#
Switch to IL17i biologic* over IL12/23i biologic, abatacept or tofacitinib
May consider alternative choices in some situations##
Switch to IL12/23i biologic* over abatacept or tofacitinib
May consider alternative choices in some situations###
Switch to Different TNFi biologic + MTX over TNFi biologic monotherapy
May consider alternative choice in some situations^
Switch to IL17i biologic monotherapy over IL17i biologic + MTX
May consider alternative choice in some situations^^
Switch to IL12/23i biologic monotherapy over IL12/23i biologic + MTX
May consider alternative choice in some situations^^^
* For each biologic, biologic monotherapy is conditionally recommended over biologic + MTX combination therapy.
# May consider alternatives, if patient has primary TNFi biologic efficacy failure (IL17i biologic, IL12/23i biologic, abatacept, tofacitinib); has TNFi biologic-associated serious adverse event (IL17i biologic, IL12/23i biologic, abatacept, tofacitinib); patients have demonstrated partial response to the current TNFi biologic therapy, especially if the TNFi biologic is a monoclonal antibody (adding MTX); prefers an oral therapy (tofacitinib); has severe psoriasis (IL17i); or prefers patient prefers less frequent drug administration (IL12/23i).
May consider alternatives (indicated in parentheses), if the patient has inflammatory bowel disease (IL12/23i biologic, tofacitinib); prefers IV dosing (abatacept); has recurrent or serious infections (abatacept); prefers an oral therapy (tofacitinib); a history of recurrent candida infections (tofacitinib); or prefers patient prefers less frequent drug administration (IL12/23i).
May consider alternatives (indicated in parentheses), if patient prefers IV dosing (abatacept); has had recurrent or serious infections (abatacept); or prefers oral therapy (tofacitinib).
^ May consider the alternative, TNFi biologic monotherapy, if patient has demonstrated MTX-associated adverse events, prefers fewer medications or perceives MTX as a burden.
^^ May consider the alternative, IL17i biologic + MTX, if patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL17i biologic was discussed as potentially beneficial to allow the new therapy time to work.
^^^ May consider the alternative, IL12/23i biologic + MTX, if patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL12/23i biologic was discussed as potentially beneficial to allow the new therapy time to work.
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Figure 5. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with a tumor necrosis factor inhibitor (TNFi) as monotherapy or as combination therapy with methotrexate (MTX). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 3 and the related section in the Results. IL-17i = interleukin-17 inhibitor; IV = intravenous.

if the patient had a partial response to the existing regimen and/or has concomitant uveitis that might respond to MTX therapy.

Active PsA despite treatment with an IL-17i biologic agent as monotherapy (Table 4 and Figure 6). *All recommendations for patients with active PsA despite IL-17i biologic treatment are conditional based on very-low-quality evidence.*

In patients with active PsA despite treatment with an IL-17i biologic, switching to a TNFi biologic is recommended over switching to an IL-12/23i biologic, adding MTX to the current IL-17i biologic, or switching to a different IL-17i biologic (Table 4 and Figure 6). Switching to an IL-12/23i biologic is recommended over adding MTX to the current IL-17i biologic or switching to a different IL-17i biologic. Treatment may be switched to an IL-12/23i biologic instead of a TNFi biologic if the patient has severe psoriasis or a contraindication to TNFi biologic treatment. Another IL-17i biologic may be used instead of switching to a TNFi or IL-12/23i biologic if the patient had a secondary efficacy failure with the current IL-17i biologic, severe psoriasis, or a contraindication to TNFi treatment. MTX may be added to the current IL-17i regimen instead of switching to a TNFi or IL-12/23i biologic in patients who have had a partial response to the current IL-17i biologic.

Active PsA despite treatment with an IL-12/23i biologic agent as monotherapy (Table 4 and Figure 6). *All recommendations for patients with active PsA despite IL-12/23i biologic treatment are conditional based on very-low-quality evidence.*

In patients with active PsA despite treatment with an IL-12/23i biologic, switching to a TNFi biologic is recommended over adding MTX to the current regimen or switching to an IL-17i biologic

Table 4. Recommendations for treatment of patients with active psoriatic arthritis despite treatment with an IL-17i or an IL-12/23i biologic monotherapy (PICOs 36–43)*

	Level of evidence†
In adult patients with active PsA despite treatment with an IL-17i biologic monotherapy,	
1. **Switch to a TNFi biologic over switching to an IL-12/23i biologic** (PICO 39) **Conditional recommendation** based on very-low-quality-evidence; may consider switching to IL- 12/23i if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Very low
2. **Switch to a TNFi biologic over switching to a different IL-17i biologic** (PICO 42) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different IL-17i if the patient had had a secondary efficacy failure to current IL-17i, or severe psoriasis, or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
3. **Switch to a TNFi biologic over adding MTX to an IL-17i biologic** (PICO 41) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX to an IL-17i if the patient had had a partial response to the existing regimen or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
4. **Switch to an IL-12/23i biologic over switching to a different IL-17i biologic** (PICO 43) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different IL-17i if the patient had had a secondary efficacy failure to current IL-17i or severe psoriasis,‡ or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
5. **Switch to an IL-12/23i biologic over adding MTX to an IL-17i biologic** (PICO 40) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX to an IL-17i if the patient had had a partial response to the existing regimen.	Very low
In adult patients with active PsA despite treatment with an IL-12/23i biologic monotherapy,	
6. **Switch to a TNFi biologic over switching to an IL-17i biologic** (PICO 38) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
7. **Switch to a TNFi biologic over adding MTX to an IL-12/23i biologic** (PICO 36) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX in patients in whom the severe psoriasis is not responding to the current therapy, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
8. **Switch to an IL-17i biologic over adding MTX to an IL-12/23i biologic** (PICO 37). **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX in patients with only partial response to the current therapy or in those who potentially have not had enough time to adequately respond.	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease. IL-17i = interleukin-17 inhibitor; TNFi = tumor necrosis factor inhibitor; MTX = methotrexate.

† When there were no published studies—as was the case with all of the recommendations presented in this table—we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

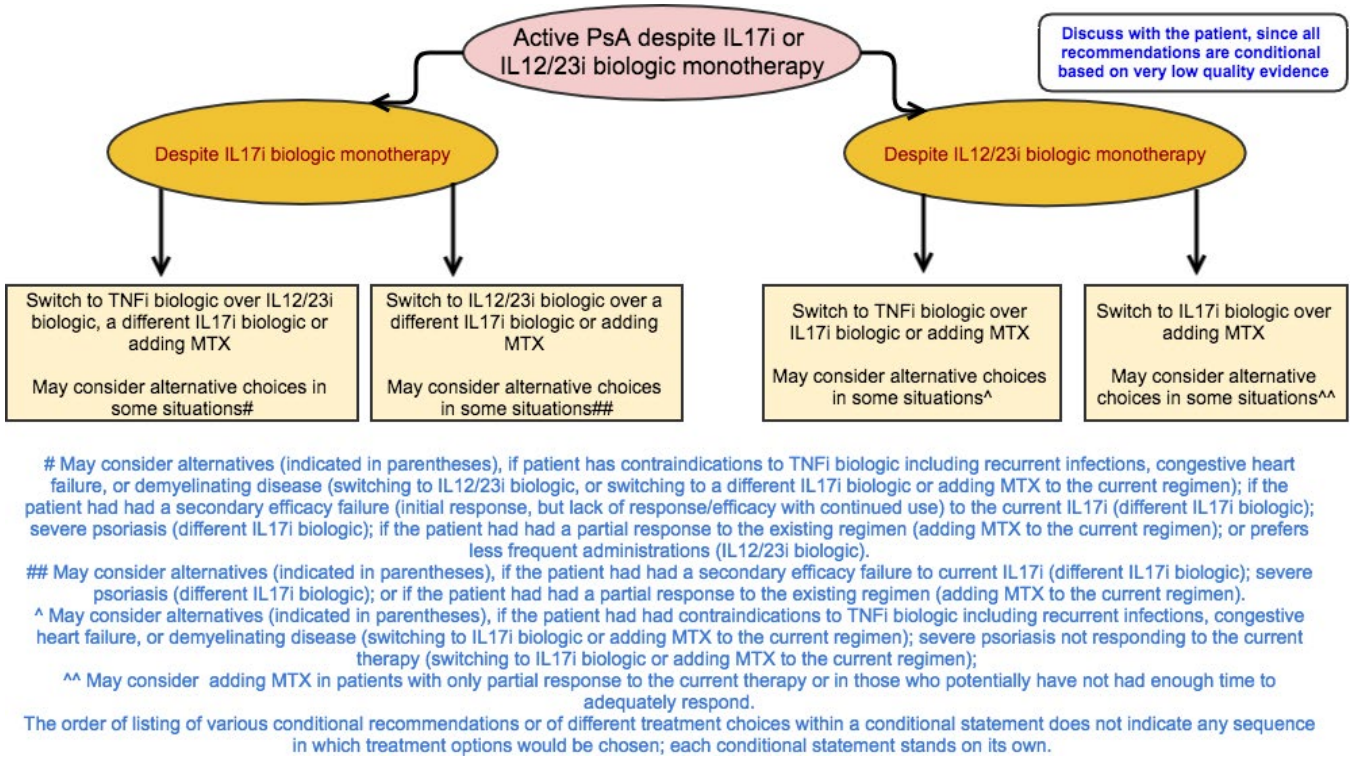
Active PsA despite IL17i or IL12/23i biologic monotherapy
Discuss with the patient, since all recommendations are conditional based on very low quality evidence
Despite IL17i biologic monotherapy
Despite IL12/23i biologic monotherapy
Switch to TNFi biologic over IL12/23i biologic, a different IL17i biologic or adding MTX
May consider alternative choices in some situations#
Switch to IL12/23i biologic over a different IL17i biologic or adding MTX
May consider alternative choices in some situations##
Switch to TNFi biologic over IL17i biologic or adding MTX
May consider alternative choices in some situations^
Switch to IL17i biologic over adding MTX
May consider alternative choices in some situations^^
May consider alternatives (indicated in parentheses), if patient has contraindications to TNFi biologic including recurrent infections, congestive heart failure, or demyelinating disease (switching to IL12/23i biologic, or switching to a different IL17i biologic or adding MTX to the current regimen); if the patient had had a secondary efficacy failure (initial response, but lack of response/efficacy with continued use) to the current IL17i (different IL17i biologic); severe psoriasis (different IL17i biologic); if the patient had had a partial response to the existing regimen (adding MTX to the current regimen); or prefers less frequent administrations (IL12/23i biologic).
May consider alternatives (indicated in parentheses), if the patient had had a secondary efficacy failure to current IL17i (different IL17i biologic); severe psoriasis (different IL17i biologic); or if the patient had had a partial response to the existing regimen (adding MTX to the current regimen).
^ May consider alternatives (indicated in parentheses), if the patient had had contraindications to TNFi biologic including recurrent infections, congestive heart failure, or demyelinating disease (switching to IL17i biologic or adding MTX to the current regimen); severe psoriasis not responding to the current therapy (switching to IL17i biologic or adding MTX to the current regimen);
^^ May consider adding MTX in patients with only partial response to the current therapy or in those who potentially have not had enough time to adequately respond.
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Figure 6. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with interleukin-17 inhibitor (IL-17i) or IL-12/23i biologic monotherapy. All recommendations are conditional based on low- to very-low-quality of evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 4 and the related section in the Results. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate.

(Table 4 and Figure 6). Switching to an IL-17i biologic is recommended over adding MTX to the current therapy. Treatment may be switched to an IL-17i biologic instead of a TNFi biologic if the patient has severe psoriasis or a contraindication to TNFi biologic treatment. MTX may be added to the current IL-12/23i biologic therapy instead of switching to a TNFi or an IL-17i biologic in patients with a partial response to the current therapy; MTX may also be added to the current IL-12/23i biologic therapy instead of switching to a TNFi biologic in the presence of contraindications to TNFi biologics.

Treat-to-target (Table 5). *This recommendation for patients with active PsA is conditional based on low-quality evidence.*

In patients with active PsA, using a treat-to-target strategy is recommended over not following a-treat-to-target strategy. One may consider not using a treat-to-target strategy in patients in whom there are concerns related to increased adverse events, costs of therapy, and patient burden of medications associated with tighter control.

Active PsA with psoriatic spondylitis/axial disease despite treatment with NSAIDs (Table 5). *All recommendations for patients with active PsA with psoriatic spondylitis/axial disease despite NSAID treatment are conditional based on very-low-quality evidence.*

The ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for patients with axial spondyloarthritis (35) should be followed for patients with axial PsA. OSMs are not effective for axial disease (35). In patients with active axial PsA despite NSAID treatment, a TNFi biologic is recommended over an IL-17i or IL-12/23i biologic, and an IL-17i biologic is recommended over an IL-12/23i biologic. An IL-17i biologic may be used instead of a TNFi biologic if the patient has severe psoriasis or a contraindication to TNFi biologic treatment (Table 5). We recommend *not using* an IL-12/23i biologic since 3 randomized trials of an IL-12/23i biologic (ustekinumab) in patients with axial spondyloarthritis (a related condition) were stopped because the key primary and secondary end points were not achieved (36–38); the safety profile was reportedly consistent with that observed in past ustekinumab studies.

Table 5. Recommendations for treatment of patients with active psoriatic arthritis including treat-to-target, active axial disease, enthesitis, or active inflammatory bowel disease (PICOs 44–55; 58–62)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA,	
1. **Use a treat-to-target strategy over not following a treat-to-target strategy** (PICO 44) **Conditional recommendation** based on low-quality evidence; may consider not following a treat-to-target strategy in patients in whom higher frequency and/or severity of adverse events, higher cost of therapy, or higher patient burden of medications with tighter control are a concern.	Low (113)
In patients with active PsA with psoriatic spondylitis/axial disease despite treatment with NSAIDs,‡	
2. **Switch to a TNFi biologic over switching to an IL-17i biologic** (PICO 46) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic if the patient has contraindications to TNFi biologics, congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or if the patient has severe psoriasis.§	Very low
3. **Switch to a TNFi biologic over switching to an IL-12/23i biologic** (PICO 45) **Conditional recommendation** based on very-low-quality evidence; switching to an IL-12/23i biologic is *not* considered since recent trials in axial SpA were stopped.	Very low
4. **Switch to an IL-17i biologic over switching to an IL-12/23i** (PICO 47) **Conditional recommendation** based on very-low-quality evidence; switching to an IL-12/23i biologic is *not* considered since recent trials in axial SpA were stopped.	Very low
In adult patients with active PsA and predominant enthesitis who are both OSM- and biologic treatment–naive,¶	
5. **Start oral NSAIDs over an OSM (specifically apremilast)** (PICO 48) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM (specifically apremilast) if the patient has active joint disease and/or skin disease or contraindications to the use of NSAIDs, including cardiovascular disease, peptic ulcer disease, or renal disease or impairment.	Very low
6. **Start a TNFi biologic over an OSM (specifically apremilast)** (PICO 48A) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM (specifically apremilast) if the patient prefers an oral treatment as the first therapy or the patient has contraindications to TNFi biologics, including recurrent infections, congestive heart failure, or demyelinating disease.	Very low
7. **Start tofacitinib over an OSM (specifically apremilast)** (PICO 55) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM (specifically apremilast) if the patient has recurrent infections.	Very low
In adult patients with active PsA and predominant enthesitis despite treatment with OSM,	
8. **Switch to a TNFi biologic over an IL-17i biologic** (PICO 53) **Conditional recommendation** based on low-quality evidence; may consider switching to an IL-117i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (72, 73, 76, 89, 90, 92)
9. **Switch to a TNFi biologic over an IL-12/23i biologic** (PICO 52) **Conditional recommendation** based on low-quality evidence; may consider switching to an IL-12/23i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or if the patient prefers less frequent drug administration.	Low (72, 73, 76, 98, 100)
10. **Switch to a TNFi biologic over switching to another OSM** (PICO 49) **Conditional recommendation** based on low-quality evidence; may consider switching to another OSM# if the patient prefers an oral medication over an injection, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (72, 73, 76, 83–85)

Table 5. *(Cont'd)*

	Level of evidence (evidence [refs.] reviewed)†
11. **Switch to an IL-17i biologic over an IL-12/23i biologic** (PICO 54) **Conditional recommendation** based on low-quality evidence; may consider switching to an IL-12/23i if the patient has concomitant IBD or if the patient prefers less frequent drug administration.	Low (89, 90, 92, 93, 98–100)
12. **Switch to an IL-17i biologic over switching to another OSM** (PICO 51) **Conditional recommendation** based on low-quality evidence; may consider switching to another OSM if the patient prefers an oral medication.	Low (83–86, 89, 90, 92, 93)
13. **Switch to an IL-12/23i biologic over switching to another OSM** (PICO 50) **Conditional recommendation** based on low-quality evidence; may consider switching to another OSM# if the patient prefers an oral medication over an injection, or if there are contraindications to an IL- 12/23i, such as severe recurrent infections.	Low (83–86, 98, 100)
In adult patients with active PsA and concomitant active IBD who are both OSM- and biologic treatment–naive,	
14. **Start a monoclonal antibody TNFi biologic over an OSM** (PICO 62) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM if the patient prefers an oral medication, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low (114)
In adult patients with active PsA and concomitant active IBD despite treatment with an OSM,	
15. **Switch to a monoclonal antibody TNFi biologic over a TNFi biologic soluble receptor biologic (i.e., etanercept)** (PICO 58)	Moderate (115–117)
Strong recommendation supported by moderate-quality evidence, showing TNFi monoclonal antibody biologics are effective in IBD but indirect evidence shows a TNFi biologic soluble receptor biologic is not effective for the treatment of IBD.	
16. **Switch to a TNFi monoclonal antibody biologic over an IL-17i biologic** (PICO 59)	Moderate (50)
Strong recommendation supported by moderate-quality evidence showing monoclonal antibody TNFi biologics are effective for IBD while an IL-17i biologic is not effective for IBD.	
17. **Switch to a TNFi biologic monoclonal antibody biologic over an IL-12/23i biologic** (PICO 61) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL- 12/23i biologic if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Very low
18. **Switch to an IL-12/23i biologic over switching to an IL-17i biologic** (PICO 60)	Moderate (50)
Strong recommendation supported by moderate-quality evidence showing IL-12/23i biologic is effective for IBD while an IL-17i biologic is not effective for IBD.	

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD).
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Axial disease is generally treated according to the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for spondyloarthritis (SpA).
§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.
¶ Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and biologic treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi,), interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.
# It should be noted that for the enthesitis questions (PICO 49, 50, and 51), the existing evidence was mainly drawn from the apremilast studies, as no randomized controlled trial report described enthesitis outcomes for the other OSMs.

Active PsA with predominant enthesitis in treatment-naive patients and despite treatment with an OSM (Table 5). *All recommendations for patients with active PsA with predominant enthesitis are conditional based on low- to very-low-quality evidence. (This section names apremilast among all OSMs specifically for recommendations, since of the OSMs, only apremilast has shown efficacy for enthesitis.)*

In treatment-naive PsA patients with predominant enthesitis, a TNFi biologic is recommended over an OSM as a first-line option. Apremilast may be used instead of a TNFi biologic if the patient prefers an oral therapy or has contraindications to TNFi. Oral NSAIDs are recommended over starting an OSM unless the patient has cardiovascular disease, peptic ulcer disease, renal disease (or impairment), or severe psoriasis or PsA, in which case apremilast may be given instead of NSAIDs. Tofacitinib is recommended over apremilast for treatment-naive patients with predominant enthesitis. Apremilast may be used instead of tofacitinib in patients with recurrent infections.

In patients with active PsA with predominant enthesitis despite treatment with an OSM (used for other manifestations of PsA), a TNFi biologic, an IL-17i biologic, or an IL-12/23i biologic is recommended over switching to another OSM. Apremilast may be used in patients who prefer oral therapy or who have recurrent infections or contraindications to TNFi biologics. A TNFi biologic is recommended over an IL-17i or IL-12/23i biologic. An IL-17i or IL-12/23i biologic may be used instead of a TNFi biologic in patients with severe psoriasis or contraindications to TNFi. An IL-17i biologic is recommended over an IL-12/23i biologic. An IL-12/23i biologic may be used instead of a TNFi biologic in patients who prefer less frequent drug administration, and instead of an IL-17i biologic in patients with concomitant IBD or who prefer less frequent drug administration.

Active PsA with concomitant active IBD (Table 5). *All recommendations for patients with active PsA with concomitant active IBD are strong based on moderate-quality evidence, except for 2 conditional recommendations based on very-low-quality evidence.*

Active PsA in OSM- and biologic treatment–naive patients with concomitant active IBD. In patients with active PsA with concomitant active IBD who have not received OSM or biologic treatment, a monoclonal antibody TNFi biologic (excludes etanercept, which is a fusion molecule/soluble receptor biologic) is recommended over an OSM (Table 5). An OSM may be used in patients without severe PsA who prefer oral therapy or have contraindications to TNFi biologics.

Active PsA despite treatment with an OSM in patients with concomitant active IBD. In patients with active PsA with concomitant active IBD despite treatment with an OSM, a monoclonal antibody TNFi biologic or an IL-12/23i biologic *should be used* over an IL-17i biologic, and a monoclonal antibody TNFi biologic *should be used* over a TNFi soluble receptor biologic (etanercept) (*all strong recommendations* [Table 5]). A monoclonal antibody TNFi biologic is recommended over an IL-12/23i biologic (conditional recommendation). An IL-12/23i biologic may be used instead of a monoclonal antibody TNFi biologic in patients with contraindications to TNFi biologics or who prefer less frequent drug administration.

Active PsA with comorbidities (Table 6). *All recommendations for patients with active PsA with comorbidities are conditional based on low- to very-low-quality evidence, except those for patients with serious infections, which are strong based on moderate-quality evidence.*

Active PsA in OSM- and biologic treatment–naive patients with concomitant diabetes. In patients with active PsA with concomitant active diabetes who have not received OSM or biologic treatment, an OSM other than MTX is recommended over a TNFi biologic, due to the concern about the higher prevalence of fatty liver disease and liver toxicity with MTX use in this patient population (39,40) (Table 6). A TNFi biologic may be used instead of an OSM in the presence of severe PsA or severe psoriasis or when diabetes is well controlled (i.e., with a potentially lower risk of infections).

Active PsA in OSM- and biologic treatment–naive patients with frequent serious infections. In patients with active PsA who have frequent serious infections and have not received OSM or biologic treatment, an OSM *should be used* over a TNFi biologic as a first-line treatment since there is a black box warning against the use of a TNFi biologic in patients with frequent serious infections (*strong recommendation*). An IL-12/23i or IL-17i biologic is recommended over a TNFi biologic (conditional recommendation [Table 6]). A TNFi biologic may be used instead of an IL-12/23i biologic in patients with severe PsA and instead of an IL-17i biologic in patients with concomitant IBD.

Active PsA in patients requiring killed or live attenuated vaccinations when starting biologic treatment (Table 7). *All recommendations for vaccinations in patients with active PsA are conditional based on very-low-quality evidence.*

It is recommended that the biologic treatment be started and the killed vaccines administered (as indicated based on patient age, sex, and immunization history per recommendations of the Centers for Disease Control and Prevention [41]) in patients with active PsA over delaying the biologic to give the killed vaccines. Delaying the start of the biologic is recommended over not delaying to administer a live attenuated vaccination in patients with active PsA (Table 7). If PsA manifestations are severe and delaying the start of the biologic is not desirable, starting the biologic and administering the live attenuated vaccines at the same time might be considered.

Table 6. Recommendations for treatment of patients with active psoriatic arthritis and comorbidities, including concomitant diabetes and recurrent serious infections (PICOs 63–66)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA and diabetes who are both OSM- and biologic treatment–naive,‡	
1. **Start an OSM other than MTX over a TNFi biologic** (PICO 63a) **Conditional recommendation** based on very-low-quality evidence; may consider starting a TNFi, if the patient has severe PsA§ or severe/active skin disease,¶ when diabetes is well controlled.	Very low (118, 119)
In adult patients with active PsA and frequent serious infections who are both OSM- and biologic treatment–naive,	
2. **Start an OSM over a TNFi biologic** (PICO 64) **Strong recommendation** supported by moderate-quality evidence, including a black box warning against the use of a TNFi biologic with regard to increased risk of serious infection.	Moderate (33, 120)
3. **Start an IL-12/23i biologic over a TNFi biologic** (PICO 65) **Conditional recommendation** based on very-low-quality evidence; may consider starting a TNFi if the patient has severe PsA.	Very low (33)
4. **Start an IL-17i biologic over a TNFi biologic** (PICO 66) **Conditional recommendation** based on very-low-quality evidence; may consider starting a TNFi biologic in patients with concomitant IBD.	Very low

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD).
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and other treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi), interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs, glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.
§ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.
¶ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

Recommendations for nonpharmacologic interventions in patients with active PsA regardless of pharmacologic treatment status (Table 8)

All recommendations for nonpharmacologic interventions for patients with active PsA are conditional based on low- to very-low-quality evidence, except that for smoking cessation, which is a strong recommendation.

It is recommended that patients with active PsA use some form or combination of exercise, physical therapy, occupational therapy, massage therapy, and acupuncture over not using these modalities as tolerated. Low-impact exercise (e.g., tai chi, yoga, swimming) is recommended over high-impact exercise (e.g., running). High-impact exercises may be performed instead of low-impact exercises by patients who prefer the former and

Table 7. Recommendations for vaccination in patients with active psoriatic arthritis (PICOs 56–57)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA needing vaccinations,‡	
1. **Start the biologic and administer killed vaccines over delaying the start of biologic to administer killed vaccines** (PICO 56) **Conditional recommendation** based on very-low-quality evidence; may consider delaying the start of biologic to administer killed vaccines due to patient preference based on patient belief about vaccine efficacy.	Very low (121–126)
2. **Delay the start of biologic to administer live attenuated vaccines over starting the biologic and administering live attenuated vaccines** (PICO 57) **Conditional recommendation** based on very-low-quality evidence; may consider starting the biologic and administering live attenuated vaccines in patients with very active severe joint§ or skin¶ disease who prefer no delay in biologic initiation.	Very low (127)

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Vaccines as indicated by patient age, sex, and immunization history per recommendations from the Centers for Disease Control and Prevention and available at: https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf.
§ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.
¶ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

have no contraindications to high-impact exercises (Table 8). Clinicians *should* encourage patients to stop smoking, offering cessation aids, due to a demonstrated effectiveness of smoking cessation in randomized trials in other conditions and in the general population (42–44) (*strong recommendation*). In PsA patients who are overweight or obese, weight loss is recommended in order to potentially increase pharmacologic response.

All strong recommendations in this guideline are also listed separately in Supplementary Appendix 6, at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract.

DISCUSSION

We present herein the first ACR/NPF guideline for the treatment of psoriatic arthritis. The goal of this guideline is to assist health care providers in managing active PsA in their patients, including optimizing therapy. PsA is a heterogeneous and multifaceted inflammatory disease, and its different clinical features (e.g., peripheral arthritis, psoriasis, nail disease, enthesitis, dactylitis, axial disease) sometimes respond differently to therapy. Despite an expansion in the number of new therapies for PsA, there remains limited comparative efficacy/effectiveness evidence to inform treatment decisions. Thus, most of our recommendations are based on low-quality evidence and are conditional. The conditional recommendations convey that, although the suggested course of action will be best for many patients, there will be some patients in whom, considering their comorbidities and/or their values and preferences, the alternative represents the best choice. The guideline will be updated as new evidence from comparative studies becomes available.

A Patient Panel meeting was held prior to the Voting Panel meeting to gain insight into patients' values and preferences for the pharmacologic/nonpharmacologic intervention comparisons being addressed. We recognize that patient preferences are an important part of our treatment recommendations. Findings from the Patient Panel meeting were discussed throughout the Voting Panel

Table 8. Recommendations for treatment of patients with active psoriatic arthritis with nonpharmacologic interventions (PICOs 1–8)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA,	
1. **Recommend exercise over no exercise** (PICO 1) **Conditional recommendation** based on low-quality evidence; may consider no exercise in patients with existing muscle/tendon injury or multiple inflamed symptomatic joints with worsening pain with exercise.	Low (128)
2. **Recommend low-impact exercise (e.g., tai chi, yoga, swimming) over high-impact exercise (e.g., running)** (PICO 2) **Conditional recommendation** based on very-low-quality evidence; may consider high-impact exercise due to patient preference.	Very low
3. **Recommend physical therapy over no physical therapy** (PICO 3) **Conditional recommendation** based on very-low-quality evidence; may consider no physical therapy due to patient preference, out-of-pocket cost, distance to physical therapy site, or lack of transportation.	Very low
4. **Recommend occupational therapy over no occupational therapy** (PICO 4) **Conditional recommendation** based on low-quality evidence; may consider no occupational therapy due to patient preference, out-of-pocket cost, distance to occupational therapy site, or lack of transportation.	Low (129, 130)
5. **Recommend weight loss over no weight loss for patients who are overweight/obese** (PICO 5) **Conditional recommendation** based on low-quality evidence; may consider no weight loss due to additional patient burden involved with weight-loss program.	Low (131–133)
6. **Recommend massage therapy over no massage therapy** (PICO 7) **Conditional recommendation** based on very-low-quality evidence; may consider no massage therapy due to associated costs.	Very low (134)
7. **Recommend acupuncture over no acupuncture** (PICO 8) **Conditional recommendation** based on very-low-quality evidence; may consider no acupuncture due to associated costs.	Very low (135)
8. **Recommend smoking cessation over no smoking cessation** (PICO 6) **Strong recommendation** supported by moderate-quality evidence, rated down for indirectness.	Moderate (136, 137)

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

meeting to ensure that patient input was incorporated into the final PsA guideline. Examples of patient feedback included strong value on therapies that are effective (e.g., prevent further damage, and improve quality of life, social participation, and function) and safe (especially having low adverse event profiles). In particular, patients discussed the negative impact of adverse events (e.g., fatigue, nausea, and malaise) on quality of life and social participation, and thus the risk for these adverse events weighed heavily in patients' decision-making. The concept of treat-to-target was challenging for patients. Although they saw value in improved outcomes, they also thought this strategy could increase costs to the patient (e.g., copayments, time traveling to more frequent appointments, etc.) and potentially increase adverse events. Therefore, a detailed conversation with the patient is needed to make decisions regarding treat-to-target. To help ensure that the recommendations were patient-centered, 2 patients were members of the Voting Panel.

While using a treat-to-target approach over not using a treat-to-target approach was discussed by the Voting Panel, we did not address specific targets to be recommended or used. There have been 2 international meetings to discuss potential targets: the use of either minimal disease activity (MDA) or disease activity in psoriatic arthritis (DAPSA) (45,46). The treatment target for PsA would likely be MDA or DAPSA, although a different target may be chosen through patient–provider discussion.

The ACR/NPF PsA guideline conditionally recommends a TNFi biologic over an OSM agent in patients with active PsA. The

available low-quality evidence is inconclusive regarding the efficacy of OSMs in management of PsA, whereas there is moderate-quality evidence of the benefits of TNFi biologics, in particular regarding their impact on the prevention of disease progression and joint damage. In making their recommendation, the panel recognized the cost implications, but put considerations of quality of evidence for benefit over other considerations. This guideline provides recommendations for early and aggressive therapy in patients with newly diagnosed PsA.

The recommendation is, however, conditional, and the panel recognized several potential exceptions to it. Circumstances in which a patient may choose an OSM over a TNFi biologic may include mild-to-moderate disease, a preference of oral over parenteral therapy, or concerns regarding adverse effects of a biologic. A TNFi biologic would not be a good choice in patients with contraindications, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.

During the development of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommendations (47) and the European League Against Rheumatism (EULAR) recommendations (48) for the treatment of PsA, panel members also challenged the decision to put OSMs first in those recommendations. For the EULAR recommendations, the final decision was made based on the lower cost of these medications, a consideration our panel placed lower than the quality of evidence for benefit.

In patients with concomitant IBD, the Voting Panel made strong recommendations favoring a monoclonal antibody TNFi or an IL-12/23i biologic over an IL-17i biologic or a TNFi receptor biologic (etanercept). This was based on moderate-quality evidence showing that TNFi biologics and ustekinumab (an IL-12/23i biologic) are effective for the management of IBD, whereas etanercept (a TNFi receptor biologic) and secukinumab (an IL-17i biologic) are not (49,50).

When the evidence was low or very-low quality, the panel could not be confident in the judgment of net benefit—thus the conditional recommendation. Often, low- or very-low-quality evidence came from indirect evidence, for instance from rheumatoid arthritis (33) or, in the absence of studies, from clinical experience (Supplementary Appendix 5, on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract). When data on comparative benefits and comparative harms were similar between two medications, the panel explicitly preferred and recommended the medication for which longer-term harms were more well-known, and in which the physician experience in patients with PsA was longer, supplementing with harms data/experience from related rheumatic conditions, where these medications are commonly used. In each case, judgments of net benefit involved explicit consideration of values and preferences, including input from Patient Panel members of the Voting Panel as well as the full Patient Panel that met prior to the Voting Panel meeting.

We recognize that these recommendations do not account for the full complexity of PsA or the full range of possible therapies (e.g., glucocorticoids were not addressed). The high degree of heterogeneity in the presentation and course of PsA coupled with the involvement of multiple domains in a single patient cannot be captured in a single algorithm. In addition, reporting of disease measures and differences in inclusion/exclusion criteria in PsA clinical trials makes it difficult to compare therapies across trials. The impact of alternative therapies on important outcomes such as joint damage still remains to be elucidated. Vaccination recommendations with tofacitinib were not included, as it was not yet approved for PsA when the PICO questions were drafted and only a limited number of PICO questions could be feasibly included for voting. Additional topics, including vaccination in the setting of tofacitinib, will be addressed in a subsequent guideline update.

The ACR has decided to use GRADE methodology in the development of guidelines for the management of rheumatic diseases. The GRADE methodology specifies that panels make recommendations based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the evidence based on the lowest quality of the critical outcomes—high, moderate, low, or very low), and patients' values and preferences. The rating of the quality of evidence for each clinical situation (PICO question) helped to inform the strength of the recommendation (strong or conditional) (51).

The use of GRADE (not used in other PsA treatment recommendations) allowed an explicit consideration of the overall evidence, including the balance of benefits and harms of treatments, the incorporation of patient values and preferences, and cost considerations to judge the tradeoff. This approach led to transparency in decision making by the Voting Panel for each clinical scenario and the formulation of these recommendations. Consistent with GRADE guidance, the Voting Panel usually offered a strong recommendation in the presence of moderate- or high-quality rating of the evidence, and a conditional recommendation in the presence of very-low or low-quality evidence (although recommendations can also be conditional in the setting of moderate-quality evidence, and in certain circumstances strong in the face of low-quality evidence) (15). The other merits of the ACR/NPF process undertaken included a comprehensive literature search, the consideration of each comparison in light of the available evidence, the diverse composition of the Voting Panel, the inclusion of all of the available therapies (e.g., IL-17i biologics, an IL-12/23i biologic, abatacept, and tofacitinib) in the decision-making process (including those approved for psoriasis or rheumatoid arthritis but not yet for PsA, ensuring that the guideline would not be out of date by the time it was published), and the inclusion of population subsets, such as those with predominant enthesitis and/or IBD.

Limitations of the guideline include the limited comparative evidence to inform selection of therapies (i.e., primary comparative benefit/efficacy and harms evidence) and the inability to include all possible clinical scenarios due to the necessity of keeping the task feasible. Because the American Academy of Dermatology and the NPF are currently developing a guideline addressing therapy for psoriasis, our guideline did not address treatment of isolated psoriasis. Another limitation is that we searched only English-language literature. The major limitation of the work arises from the limitations in the evidence.

In this guideline, we often used indirect comparisons among trials/therapies, frequently relying on network meta-analysis. Stratified analyses among subgroups (e.g., treatment-naive, inadequate response to a TNFi biologic agent) were rarely reported separately in primary trials, limiting our ability to perform network meta-analyses in these important subgroups. For most clinical scenarios (PICO questions) there were few or no head-to-head comparison studies identified in the literature review. Thus, the quality of evidence was most often low or very low, and only occasionally moderate (Supplementary Appendix 5; http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract). This led to nearly all recommendations being conditional, with a few strong recommendations in cases in which there was sufficient evidence (including that from outside of PsA) to make the Voting Panel confident in selecting one option over the comparator. A flow chart or ranking of treatments requires strong recommendation; when recommendations are conditional/weak it means that the right course of action differs between patients. When the right course of action differs between patients, it is inappropriate to make the flow chart and establish treatment ranking or a hierarchy of treatment options (14).

The 2018 ACR/NPF guideline for the treatment of PsA will assist patients and their health care providers in making challenging disease management decisions. More comparative data are needed to inform treatment selection. Several ongoing trials, including a trial to compare a TNFi biologic combination therapy with a TNFi biologic monotherapy and MTX monotherapy (52), will inform treatment decisions. We anticipate future updates to the guideline when new evidence is available.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Singh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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2019 update of the EULAR recommendations for the management of systemic lupus erythematosus

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ABSTRACT

Our objective was to update the EULAR recommendations for the management of systemic lupus erythematosus (SLE), based on emerging new evidence. We performed a systematic literature review (01/2007–12/2017), followed by modified Delphi method, to form questions, elicit expert opinions and reach consensus. Treatment in SLE aims at remission or low disease activity and prevention of flares. Hydroxychloroquine is recommended in all patients with lupus, at a dose not exceeding 5 mg/kg real body weight. During chronic maintenance treatment, glucocorticoids (GC) should be minimised to less than 7.5 mg/day (prednisone equivalent) and, when possible, withdrawn. Appropriate initiation of immunomodulatory agents (methotrexate, azathioprine, mycophenolate) can expedite the tapering/discontinuation of GC. In persistently active or flaring extrarenal disease, add-on belimumab should be considered; rituximab (RTX) may be considered in organ-threatening, refractory disease. Updated specific recommendations are also provided for cutaneous, neuropsychiatric, haematological and renal disease. Patients with SLE should be assessed for their antiphospholipid antibody status, infectious and cardiovascular diseases risk profile and preventative strategies be tailored accordingly. The updated recommendations provide physicians and patients with updated consensus guidance on the management of SLE, combining evidence-base and expert-opinion.

INTRODUCTION

Systemic lupus erythematosus (SLE) has variable presentation, course and prognosis. The wide acceptance and popularity of the first EULAR recommendations for its management, published in 2008,[1] prompted the subsequent development of specific recommendations regarding monitoring, neuropsychiatric and renal disease, as well as for pregnancy and women's health in lupus.[2–5] Since these publications, new data have emerged on treatment strategies and validated goals of treatment, alternative regimens of glucocorticoids (GC), 'multitargeted' therapy with the use of calcineurin inhibitors (CNIs) in lupus nephritis (LN), and the approval of the first biological therapy for SLE. These advances called for an update of the EULAR recommendations for lupus, capitalising on the strengths of and experience from the previous projects.[6]

METHODS

After approval by the EULAR Executive Committee, the convenor (DB) and methodologist (GB) invited a Task Force to work on this update; two fellows (AF, MK) undertook the systematic literature review (SLR). The EULAR standardised operating procedures[7] and the Appraisal of Guidelines Research and Evaluation instrument (AGREE II)[8] were followed. Applying a Delphi-based methodology, 14 research questions were selected for SLR (online supplementary table 1). PubMed was screened using strings of relevant terms. Since this was an update of the previous 2007 recommendations, the SLR considered all English-language publications from 01/2007 until 12/2017, *with two exceptions*: (1) treatment of skin disease, where an unrestricted date search was performed and (2) renal disease, where search was limited to the period 01/2012–12/2017 (since the EULAR recommendations for LN were published in 2012). Pertinent articles, identified by manual search within the reference list of the originally retrieved publications, were also included. All retrieved items were refined based on article type, abstract, full-text content and number of included patients. The final level of evidence and grading of recommendations considered also the body of evidence that had informed the previous sets of EULAR recommendations for the management of SLE, as the convenor, methodologist and several of the panellists had also participated in the latter. A detailed presentation of the SLR results is given in online supplementary tables 2 and 3. Evidence was categorised based on the design and validity of available studies and the strength of the statements was graded (see online supplementary table 4). After rounds of discussions, the committee reached a consensus of 33 final statements, grouped in four broad categories (Goals of Treatment, Treatment of SLE, Specific manifestations, Comorbidities—table 1). Each Task Force member rated their agreement with each statement.

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Table 1 Recommendations for the management of patients with systemic lupus erythematosus

Overarching principles

- SLE is a multisystem disease—occasionally limited to one or few organs—diagnosed on clinical grounds in the presence of characteristic serological abnormalities.
- SLE care is multidisciplinary, based on a shared patient-physician decision, and should consider individual, medical and societal costs.
- Treatment of organ-threatening/life-threatening SLE includes an initial period of high-intensity immunosuppressive therapy to control disease activity, followed by a longer period of less intensive therapy to consolidate response and prevent relapses.
- Treatment goals include long-term patient survival, prevention of organ damage and optimisation of health-related quality of life.

Recommendation/Statement	Level of agreement, mean (SD)
1. Goals of treatment	
1.1 Treatment in SLE should aim at remission or low disease activity (**2b/B**) and prevention of flares (**2b/B**) in all organs, maintained with the lowest possible dose of glucocorticoids.	10.0 (0)
1.2 Flares of SLE can be treated according to the severity of organ(s) involvement by adjusting ongoing therapies (glucocorticoids, immunomodulating agents) to higher doses, switching or adding new therapies (**2b/C**).	9.95 (0.22)
2. Treatment of SLE	
2.1 HCQ	
2.1.1 HCQ is recommended for all patients with SLE (**1b/A**), unless contraindicated, at a dose not exceeding 5 mg/kg/real BW (**3b/C**).	9.65 (1.11)
2.1.2 In the absence of risk factors for retinal toxicity, ophthalmological screening (by visual fields examination and/or spectral domain-optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter (**2b/B**).	9.75 (0.70)
2.2 GC	
2.2.1 GC can be used at doses and route of administration that depend on the type and severity of organ involvement (**2b/C**).	9.95 (0.22)
2.2.2 Pulses of intravenous methylprednisolone (usually 250–1000 mg per day, for 1–3 days) provide immediate therapeutic effect and enable the use of lower starting dose of oral GC (**3b/C**).	9.85 (0.36)
2.2.3 For chronic maintenance treatment, GC should be minimised to less than 7.5 mg/day (prednisone equivalent) (**1b/B**) and, when possible, withdrawn.	9.65 (0.65)
2.2.4 Prompt initiation of immunomodulatory agents can expedite the tapering/discontinuation of GC (**2b/B**).	9.90 (0.30)
2.3 Immunosuppressive therapies	
2.3.1 In patients not responding to HCQ (alone or in combination with GC) or patients unable to reduce GC below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as *methotrexate*, **(1b/B)** *azathioprine* **(2b/C)** or *mycophenolate* **(2a/B)** should be considered.	9.85 (0.48)
2.3.2 Immunomodulating/immunosuppressive agents can be included in the initial therapy in cases of organ-threatening disease (**2b/C**).	9.85 (0.48)
2.3.3 *Cyclophosphamide* can be used for severe organ-threatening or life-threatening SLE as well as 'rescue' therapy in patients not responding to other immunosuppressive agents (**2b/C**).	9.90 (0.30)
2.4 Biologics	
2.4.1 In patients with inadequate response to standard-of-care (combinations of HCQ and GC with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses, add-on treatment with *belimumab* should be considered (**1a/A**).	9.20 (0.81)
2.4.2 In organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents, *rituximab* can be considered (**2b/C**).	9.85 (0.48)
3 Specific manifestations	
3.1 Skin disease	
3.1.1 First-line treatment of skin disease in SLE includes *topical agents* (GC, calcineurin inhibitors) (**2b/B**), *antimalarials* (HCQ, quinacrine) (**1a/A**) and/or *systemic GC* (**4/C**).	10.0 (0)
3.1.2 In non-responsive cases or cases requiring high-dose GC, *methotrexate* **(3a/B)**, *retinoids* **(4/C),** *dapsone* **(4/C)** or *mycophenolate* **(4/C)** can be added.	9.85 (0.48)
3.2 Neuropsychiatric disease	
3.2.1 *Attribution* to SLE—as opposed to non-SLE—related neuropsychiatric manifestations, is essential and can be facilitated by neuroimaging, investigation of cerebrospinal fluid, consideration of risk factors (type and timing of the manifestation in relation to the onset of lupus, patient age, non-neurological lupus activity, presence of aPL) and exclusion of confounding factors (**2b/C**).	9.65 (0.85)
3.2.2 *Treatment* of SLE-related neuropsychiatric disease includes glucocorticoids/immunosuppressive agents for manifestations considered to reflect an inflammatory process (**1b/A**), and antiplatelet/anticoagulants for atherothrombotic/aPL-related manifestations (**2b/C**).	9.85 (0.48)
3.3 Haematological disease	
3.3.1 *Acute treatment* of lupus thrombocytopenia includes high-dose GC (including pulses of intravenous methylprednisolone) (**4/C**) and/or intravenous immunoglobulin G (**4/C**).	9.95 (0.22)
3.3.2 For maintenance of response, immunosuppressive/GC-sparing agents such as *mycophenolate* **(2b/C)**, *azathioprine* **(2b/C)** or *cyclosporine* **(4/C)** can be used.	9.75 (0.62)
3.3.3 Refractory cases can be treated with *rituximab* **(3a/C)** or *cyclophosphamide* **(4/C)**.	9.65 (0.73)
3.4 Renal disease	
3.4.1 Early recognition of signs of renal involvement and—when present—performance of a diagnostic renal biopsy are essential to ensure optimal outcomes (2b/B).	9.95 (0.22)
3.4.2 *Mycophenolate* **(1a/A)** or *low-dose intravenous cyclophosphamide* **(2a/B)** are recommended as initial (induction) treatment, as they have the best efficacy/toxicity ratio.	9.85 (0.36)
3.4.3 In patients at high risk for renal failure (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis], similar regimens may be considered but high-dose intravenous cyclophosphamide can also be used (**1b/A**).	9.45 (0.80)
3.4.4 For maintenance therapy, *mycophenolate* **(1a/A)** or *azathioprine* **(1a/A)** should be used.	9.75 (0.62)

Continued

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Table 1 Continued

Recommendation/Statement	Level of agreement, mean (SD)
3.4.5 In cases with stable/improved renal function but *incomplete renal response* (persistent proteinuria >0.8–1 g/24 hours after at least 1 year of immunosuppressive treatment), *repeat biopsy* can distinguish chronic from active kidney lesions (**4/C**).	9.85 (0.48)
3.4.6 Mycophenolate may be combined with low dose of a calcineurin inhibitor in severe nephrotic syndrome (**2b/C**) or incomplete renal response (**4/C**), in the absence of uncontrolled hypertension, high chronicity index at kidney biopsy and/or reduced GFR.	9.50 (0.81)
4 Comorbidities	
4.1 Antiphospholipid syndrome	
4.1.1 All patients with SLE should be screened at diagnosis for aPL (**1a/A**).	10.0 (0)
4.1.2 Patients with SLE with high-risk aPL profile (persistently positive medium/high titres or multiple positivity) may receive primary prophylaxis with antiplatelet agents (**2a/C**), especially if other atherosclerotic/thrombophilic factors are present, after balancing the bleeding hazard.	9.45 (0.80)
4.1.3 For secondary prevention (thrombosis, pregnancy complication/loss), the therapeutic approach should be the same as for primary antiphospholipid syndrome (**1b/B**).	10.0 (0)
4.2 Infectious diseases	
4.2.1 Patients with SLE should be assessed for *general and disease-related risk factors* for infections, such as advanced age/frailty (**–/D**), diabetes mellitus (**–/D**), renal involvement (**2b/B**), immunosuppressive/biological therapy (**1b-2b/B-C**) and use of GC (**1a/A**).	9.85 (0.65)
4.2.2 General preventative measures (including immunisations) and early recognition and treatment of infection/sepsis are recommended (**–/D**).	9.90 (0.44)
4.3 Cardiovascular disease	
4.3.1 Patients with SLE should undergo regular assessment for *traditional* (**1b/B-C**) and *disease-related risk factors* for cardiovascular disease, including persistently active disease (**1b/B**), increased disease duration (**1b/A**), medium/high titres of aPL (**1b/A**), renal involvement (**1b/B**) (especially, persistent proteinuria and/or GFR <60 mL/min) and chronic use of GC (**1b/B**).	9.85 (0.65)
4.3.2 Based on their individual cardiovascular risk profile, patients with SLE may be candidates for preventative strategies as in the general population, including *low-dose aspirin* (**2b/D**) and/or *lipid-lowering agents* (**2b/D**).	9.85 (0.48)

aPL, antiphospholipid antibodies; GC, glucocorticoids; GFR, glomerular filtration rate; HCQ, hydroxychloroquine; SLE, systemic lupus erythematosus.

RESULTS AND DISCUSSION

Overarching principles

SLE represents a challenge for the treating physician in terms of diagnosis and treatment. Its protean manifestations, often multisystem but occasionally limited to a few or single organ, have led some physicians to focus exclusively on evidence of serological autoimmunity (antinuclear and more specific autoantibodies), for a disease where diagnosis is clinical after excluding competing diagnoses. Monitoring of SLE through validated disease activity and chronicity indices, including physician global assessment (PGA), is recommended. For patients with severe disease, multidisciplinary care in dedicated lupus centres is desirable.[9] Immunosuppressive (IS) therapy (for induction and maintenance of remission) is indicated in organ-threatening lupus.

Recommendations

Goals of treatment

To improve long-term patient outcomes, management should aim at remission of disease symptoms and signs, prevention of damage accrual and minimisation of drug side-effects, as well as improvement of quality of life.[10 11] *Complete remission* (absence of clinical activity with no use of GC and IS drugs) is infrequent.[12–16] To this end, newly defined low disease activity states (based on a SLEDAI score ≤3 on antimalarials, or alternatively SLEDAI ≤4, PGA≤1 with GC ≤7.5 mg of prednisone and well tolerated IS agents) have shown comparable rates with remission, regarding halting of damage accrual (OR 0.5–0.7 for increase in damage index) and prevention of flares.[14 17–20] Accordingly, treatment in SLE should aim at remission or, if this state cannot be achieved, at low disease activity in all organ systems. In LN, therapy should aim at least *partial remission* (defined as ≥50% reduction in proteinuria [UPr] to subnephrotic levels and serum creatinine [SCr] within 10% from baseline) by 6–12 months; *complete renal remission* (proteinuria <500 mg/24 hours and SCr within 10% from baseline), however, may require longer treatment duration, often more than 12 and until 24 months. In monitoring renal response, reduction of UPr (to less than 0.8 g/day) following treatment is more important than residual haematuria.[21] Patients with more severe proteinuria and longer-standing disease are less likely to respond or show more delayed responses.[22 23]

Prevention of disease flares is an additional milestone of SLE treatment. Although a universally accepted definition is lacking, most experts agree that a flare is a measurable increase in disease activity usually leading to change of treatment.[24] Flares are common in the disease course and contribute significantly to organ damage accrual and worse outcome.[17 25 26] Consistently reported risk factors for a higher disease flare rate include younger age at disease onset, no use of antimalarials, persistent generalised disease activity and serological activity (anti-dsDNA, low complement).[27–31] Assessment of adherence to drug treatment, close monitoring and optimisation of disease control in these patients may reduce the risk for a flare.

Treatment of SLE

Hydroxychloroquine

Hydroxychloroquine (HCQ) is recommended for all patients with SLE. There is evidence for multiple beneficial effects of HCQ in SLE,[32] yet poor adherence to treatment is not uncommon.[33–35] Drug blood levels can be used to assess compliance,[33 35] but data are currently insufficient to recommend routine monitoring of drug levels. Concerns for retinal toxicity with long-term HCQ therapy led to the use of more sensitive screening techniques, with a prevalence of retinal abnormalities exceeding 10% after 20 years of continuous use.[36 37] Major risk factors for retinopathy include duration of treatment (OR 4.71 for every 5 years of use), dose (OR 3.34 for every 100 mg daily dose), chronic kidney disease (adjusted OR 8.56) and pre-existing retinal or macular disease.[37] Based on existing evidence suggesting that the risk of toxicity is very low for doses below 5 mg/kg real body weight, the daily dose should not exceed this threshold. Of note, efficacy of HCQ in lupus has been established in studies

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with a prescribed dose of 6.5 mg/kg/day, thus it remains to be confirmed whether a lower dose will have comparable clinical effects. Patients in long-standing remission may have their dose lowered, although no studies have formally addressed this strategy. The choice of quinacrine, an alternative antimalarial, can be considered in patients with cutaneous manifestations and HCQ-induced retinal toxicity.

Glucocorticoids

GC can provide rapid symptom relief, but the medium to long-term aim should be to minimise daily dose to ≤7.5 mg/day prednisone equivalent or to discontinue them, because long-term GC therapy can have various detrimental effects including irreversible organ damage.[38–41] Risks are substantially increased at continuous GC doses above 7.5 mg/day, with some studies suggesting that also lower doses might be harmful.[17 42–44] To this end, two approaches can be considered: (1) use of pulses of intravenous methylprednisolone (MP) of various doses (depending on severity and body weight), which take advantage of the rapid non-genomic effects of GC[45] and may allow for a lower starting dose and faster tapering of PO GC,[46 47] and (2) early initiation of IS agents, to facilitate tapering and eventual discontinuation of oral GC (*see below*). High-dose intravenous MP (usually 250–1000 mg/day for 3 days) is often used in acute, organ-threatening disease (eg, renal, neuropsychiatric) after excluding infections.[48]

Immunosuppressive (IS) drugs

Consequent initiation of IS drugs facilitates a more rapid GC tapering and may prevent disease flares.[49] The choice of agent depends on prevailing disease manifestation(s), patient age and childbearing potential, safety concerns and cost. Methotrexate (MTX) and azathioprine (AZA) should be considered in patients with poor symptom control after a trial with GC and HCQ or when HCQ alone is unlikely to be sufficient, due to the large experience gained with their use and their relatively safe profile.[50] Published evidence is generally stronger for MTX than AZA, yet the latter is compatible with pregnancy contemplation. Mycophenolate mofetil (MMF) is a potent immunosuppressant with efficacy in renal and non-renal lupus (although not in neuropsychiatric disease).[51–53] In a recent randomised, open-label trial in extrarenal SLE, enteric-coated mycophenolate sodium (EC-MPS) was superior to AZA in achieving remission and reducing flares.[54] However, its teratogenic potential (needs to be discontinued at least 6 weeks before conceiving), along with its higher cost compared with AZA or MTX, poses a limitation towards universal recommendation in women of reproductive age with non-renal manifestations. Cyclophosphamide (CYC) can be considered in organ-threatening disease (especially renal, cardiopulmonary or neuropsychiatric) and only as rescue therapy in refractory non-major organ manifestations; due to its gonadotoxic effects, it should be used with caution in women and men of fertile age.[55–57] Concomitant use of GnRH analogues attenuates the depletion of ovarian reserve associated with CYC therapy and is recommended in premenopausal patients with SLE.[4 58 59] Information about the possibility of ovarian cryopreservation should be offered ahead of treatment. Other risks of CYC therapy such as malignancy and infections should also be considered.[60 61]

Biological agents

There is evidence to support beneficial effects of B-cell targeting agents in SLE.[62–66] Belimumab should be considered in extrarenal disease with inadequate control (ongoing disease activity or frequent flares) to first-line treatments (typically including combination of HCQ and prednisone with or without IS agents), and inability to taper GC daily dose to acceptable levels (ie, maximum 7.5 mg/day). Patients with persistent disease may benefit from belimumab; more likely to respond are patients with high disease activity (eg, SLEDAI >10), prednisone dose >7.5 mg/day and serological activity (low C3/C4, high anti-dsDNA titres), with cutaneous, musculoskeletal and serological manifestations responding the most.[67–69]

Due to the negative results of randomised controlled trials (RCTs), RTX is currently only used off-label, in patients with severe renal or extrarenal (mainly haematological and neuropsychiatric) disease refractory to other IS agents and/or belimumab, or in patients with contraindications to these drugs. As a general rule, more than one IS drug need to have failed prior to RTX administration,[70–73] except perhaps for cases of severe autoimmune thrombocytopaenia and haemolytic anaemia, where RTX has demonstrated efficacy both in lupus and in patients with isolated immune thrombocytopaenia (ITP).[74–76] In LN, RTX is typically considered following failure of first-line therapies (CYC, MMF) or in relapsing disease.[70 77] More recently, a *posthoc* analysis of the LUNAR trial showed that complete B-cell depletion following RTX treatment in LN was associated with higher odds for complete response at 78 weeks.[78]

Figure 1 summarises the various drugs used in the treatment of SLE, according to disease severity stratification. Online supplementary table 5 outlines the recommended doses of the drugs mentioned in the manuscript.

Specific manifestations

Skin disease

A large body of evidence originates from studies in patients with cutaneous lupus erythematosus (CLE). Effective protection from ultraviolet exposure with broad-spectrum sunscreens and smoking cessation are strongly recommended.[79–81] In atypical or refractory cases, a diagnostic skin biopsy should be considered. First-line treatment of skin disease includes topical agents (GC and/or CNIs) and antimalarials, with or without systemic GC (the latter at a starting dose depending on severity of skin involvement).[82 83] HCQ is the antimalarial of choice over chloroquine due to its multiple beneficial effects and possibly lower risk for retinal toxicity;[84] in cases of inadequate response or evidence of toxic retinopathy, quinacrine (mepacrine) may be used as an add-on or sequential therapy, respectively.[85–87] Although quinacrine is currently unavailable in several countries worldwide, it is a useful alternative when available. There are no studies examining retinal toxicity of quinacrine with the newer, more sensitive screening techniques (visual fields or optical coherence tomography); however with current knowledge, retinopathy is not considered a side-effect of quinacrine.

A sizeable proportion (almost 40%) of patients will not respond to first-line treatment.[86 88] In such cases, MTX can be added.[50 89] Other agents include retinoids, dapsone and MMF or EC-mycophenolic acid.[79 90 91] Belimumab and RTX have also shown efficacy in mucocutaneous manifestations of SLE, although these studies have not included a validated activity score for skin lesions; RTX may be less efficacious in chronic forms of skin lupus.[62 92–94] Thalidomide is effective in various subtypes of cutaneous disease.[95 96] Due to its strict contraindication in pregnancy, the risk for irreversible polyneuropathy, and the frequent relapses on drug discontinuation, it should be considered only as a 'rescue' therapy in patients who have failed

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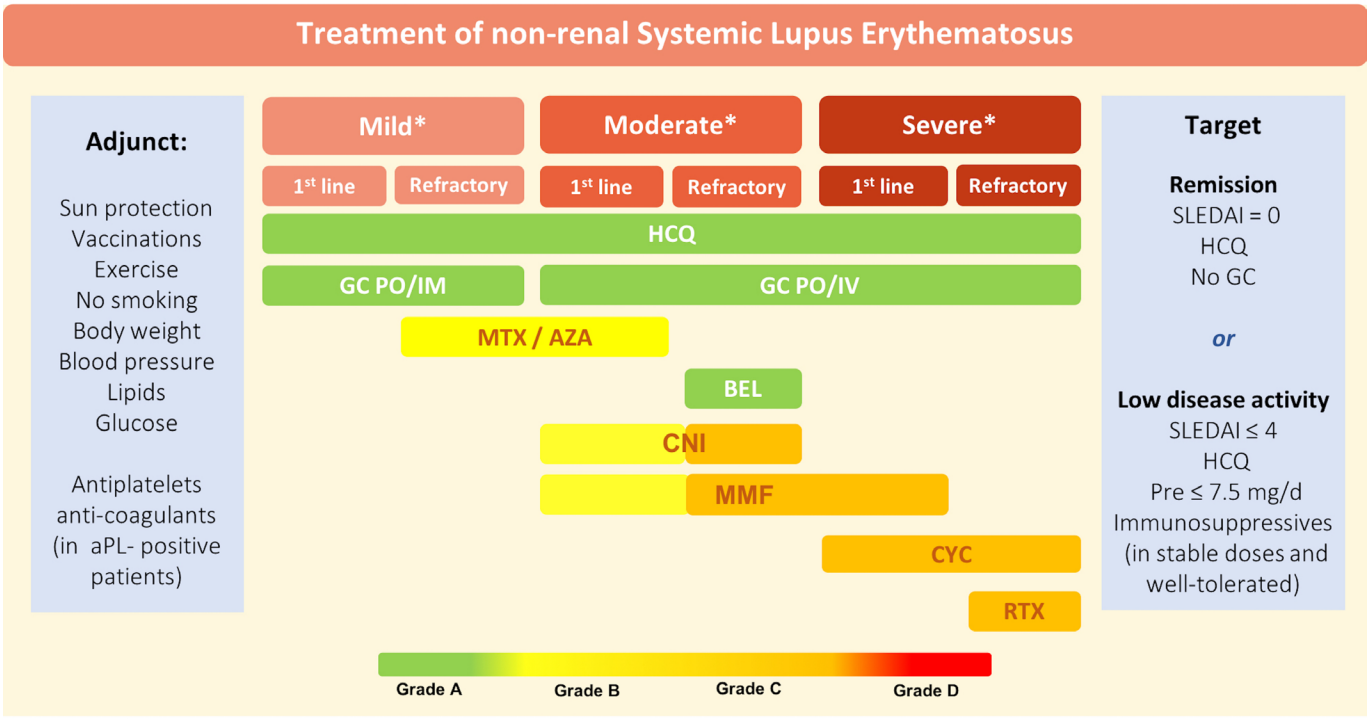

Mild: constitutional symptoms/ mild arthritis/ rash ≤9% BSA/PLTs 50-100 x 10^3/mm^3; SLEDAI≤6; BILAG C or ≤1 BILAG B manifestation
Moderate: RA-like arthritis/ rash 9-18% BSA/cutaneous vasculitis ≤18% BSA; PLTs 20-50x103/mm3/serositis; SLEDAI 7-12; ≥2 BILAG B manifestations
Severe: major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets <20x103/mm3; TTP-like disease or acute hemophagocytic syndrome; SLEDAI>12; ≥1 BILAG A manifestations

Figure 1 Treatment of non-renal SLE—recommended drugs with respective grading of recommendation. aPL, antiphospholipid antibodies; AZA, azathioprine; BEL, belimumab; BILAG: British Isles Lupus Assessment Group disease activity index; CNIs, calcineurin inhibitors; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; IM, intramuscular; MMF, mycophenolate mofetil; MTX, methotrexate; Pre, prednisone; PO, per os; RTX, rituximab; PLTs: Platelets; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

multiple previous agents. A treatment algorithm for the various subtypes of CLE has been published by a European group of Dermatologists guided by the European Dermatology Forum in cooperation with the European Academy of Dermatology and Venereology.[79]

Neuropsychiatric disease (NPSLE)

Attribution of neuropsychiatric manifestations to SLE often requires a comprehensive, multidisciplinary approach to rule out mimics (infections, malignancy and others), taking into account the presence of risk (‘*favouring*’) factors (type and timing of manifestation, presence of generalised, non-neurological disease activity, abnormal neuroimaging and cerebrospinal fluid analysis, positive antiphospholipid antibodies [aPL]),[97] as well as confounding factors favouring alternative diagnoses.[98] The use of validated attribution models may aid in the diagnostic process.[99 100]

Treatment of NPSLE depends on whether the underlying pathophysiological mechanism is presumed to be inflammatory or embolic/thrombotic/ischaemic.[2 101] GC and/or IS agents should be considered in the former, while anticoagulant/antithrombotic treatment is favoured when aPL antibodies are present.[102–107] Distinction between the two pathophysiological processes may not be easy in clinical practice, or the two processes may coexist in the same patient.[2] Combination of IS and anticoagulant/antithrombotic therapy may be considered in these patients. Patients with SLE with cerebrovascular disease should be managed like the general population in the acute phase; in addition to controlling extra-CNS lupus activity, IS therapy may be considered in the absence of aPL antibodies and other atherosclerotic risk factors or in recurrent cerebrovascular events.[108] In this context, neuroimaging and/or CSF studies may provide additional supporting evidence for IS therapy. Targeted symptomatic therapy is indicated according to the type of manifestation (eg, antipsychotics for psychosis, anxiolytics for anxiety disorder and so on).

Haematological disease

Haematological manifestations frequently necessitating anti-inflammatory/IS treatment in patients with SLE include thrombocytopaenia and autoimmune haemolytic anaemia (AIHA). First-line treatment of significant lupus thrombocytopaenia (platelet count below 30 000/mm^3) consists of moderate/high doses of GC in combination with IS agent (AZA, MMF or cyclosporine; the latter having the least potential for myelotoxicity) to facilitate GC-sparing. Initial therapy with pulses of intravenous MP (1–3 days) is encouraged. Intravenous immunoglobulin (IVIG) may be considered in the acute phase, in cases of inadequate response to high-dose GC or to avoid GC-related infectious complications.

Treatment of thrombocytopenia is typically lengthy and often characterised by relapses during GC tapering.[109] In patients with no response to GC (ie, failure to reach a platelet count >50 000/mm^3) or relapses, RTX should be considered, considering also its efficacy in ITP.[74 76 110] CYC may also be considered in such cases. Thrombopoietin agonists or splenectomy should be reserved as last options.[111 112] Autoimmune haemolytic anaemia (AIHA) is far less common than thrombocytopenia in SLE; its treatment follows the same principles regarding use of GC, IS drugs and RTX. Autoimmune leucopaenia is common in SLE but rarely needs treatment; careful work-up is recommended to exclude other causes of leucopaenia (especially drug-induced).

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Renal disease

Patients at high risk of developing renal involvement (males, juvenile lupus onset, serologically active including positivity for anti-C1q antibodies)[113–115] should be under vigilant monitoring (eg, at least every 3 months) to detect early signs of kidney disease. Following diagnosis, secured with a kidney biopsy, treatment of LN includes an initial induction phase, followed by a more prolonged maintenance phase. MMF and CYC are the IS agents of choice for induction treatment; low-dose CYC (Euro-Lupus regimen, online supplementary table 5) is preferred over high-dose CYC as it has comparable efficacy and lower risk of gonadotoxicity.[57 116 117] Published data support the use of MMF and high-dose CYC (online supplementary table 5) in severe forms of LN associated with increased risk of progression into end-stage renal disease (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis).[118 119] An early significant drop in UPr (to ≤1 g/day at 6 months or ≤0.8 g/day at 12 months) is a predictor of favourable long-term renal outcome.[21 117 120] MMF or AZA may be used as maintenance therapy, with the former associated with fewer relapses;[121 122] the choice depends on the agent used for induction phase and on patient characteristics, including age, race and wish for pregnancy. In refractory or relapsing disease, RTX may be considered.

Following the EULAR recommendations for LN in 2012, several studies have been published regarding the use of CNIs to treat proliferative LN, either alone or in the form of a 'multi-target therapy' (combination of tacrolimus with MMF).[123–127] These studies were performed almost exclusively in Asian populations and had short follow-up; hence, data have to be corroborated with longer duration studies in multiethnic populations. To this end, at present, CNIs may be considered as second-line agents for induction or maintenance therapy mainly in membranous LN, podocytopathy, or in proliferative disease with refractory nephrotic syndrome, despite standard-of-care within 3–6 months;[128 129] in the latter case, they may be used alone or in combination with MMF, since small, observational studies have shown the CNI/MMF combination to be effective in disease refractory to standard therapy.[130–132] Monitoring SCr and blood levels of CNI to avoid chronic drug toxicity is essential.

Comorbidities

Antiphospholipid antibodies (aPL) and antiphospholipid syndrome (APS)

The presence of aPL is associated with thrombotic and obstetric complications and increased risk of damage accrual.[133 134] In aPL carriers, a recent meta-analysis supported a protective role of low-dose aspirin for primary prophylaxis against thrombosis in the subgroup of aPL carriers who had SLE;[135] however, in view of the potential bleeding hazard,[136 137] it is not clear whether this should be applied to patients with lupus with any aPL antibodies or only to those carrying a high risk aPL profile (ie, triple aPL positivity, lupus anticoagulant or high titres of anticardiolipin antibodies).[138] Patients with SLE with aPL may also receive additional anticoagulant treatment, such as low-molecular weight heparin, during high-risk periods for thrombosis (pregnancy or postoperatively), although no studies have formally addressed this question.

No studies have been performed exclusively on patients with SLE-APS, with several studies excluding secondary APS due to lupus. Thus, with current knowledge, treatment of APS in the context of SLE should not differ from treatment of primary APS. A recent randomised, open-label trial comparing rivaroxaban to warfarin in APS with triple aPL positivity (~21% of patients had SLE-APS) was prematurely terminated due to an excess of thromboembolic events in the rivaroxaban arm.[139] Thus, in patients with SLE-APS, use of novel oral anticoagulants for secondary prevention should be avoided; however, they could potentially serve as an alternative option in selected patients (low-risk aPL profile, no history of arterial thrombotic events) with difficult to control international normalised ratio on warfarin, after balancing possible risks.

Infections

Risk of infection in SLE is associated with both disease-related and treatment-related factors; high-dose GC therapy, CYC, MMF and RTX are all associated with an increased risk for infection, while high disease activity, severe leucopaenia and presence of renal involvement (±hypogammaglobulinaemia in nephrotic syndrome) also contribute independently.[48 140–143] Protection against infections should be proactive, focusing both on primary prevention, as well as timely recognition and treatment. Patients with lupus should receive vaccinations according to the EULAR recommendations for vaccination of patients with autoimmune rheumatic diseases.[144 145] Immunisation against seasonal influenza and pneumococcal infection (both PCV13 and PPSV23) should be strongly considered, preferably during stable disease. Herpes zoster vaccination is now available for the general population, but a study in SLE has not been performed. Prompt diagnosis and treatment of sepsis is essential. To this end, validated scores such as the quick SOFA ([systolic blood pressure ≤100 mm Hg, respiratory rate ≥22/min, altered mental state with Glasgow coma scale <15]: the presence of ≥2 points near the onset of infection is associated with a greater risk of death or prolonged intensive care unit stay] may identify patients who are at greater risk for a poor outcome.[146]

Cardiovascular disease

SLE is an independent risk factor for cardiovascular disease (CVD), due to both traditional and disease-related risk factors, such as persistent disease activity, LN, presence of aPL and use of GC.[147–149] Surrogate measures of atherosclerosis, such as carotid plaques, carotid intima media thickness (cIMT) and coronary artery calcium are frequently used to identify subclinical CVD in SLE.[150] Low-dose aspirin may be considered for primary prevention of CVD, as it may reduce the risk for incident CVD in SLE (HR 0.24 in one retrospective study).[151 152] However, this has to be viewed in light of recent large studies in diabetics and elderly showing that the benefits of aspirin for primary CVD prevention are counterbalanced by the larger bleeding hazard.[136 153] The value of statins in SLE has been tested in RCTs, which failed to show a clear benefit over placebo, when cIMT was used a surrogate marker for CVD.[154 155] Thus, routine use of statins is not recommended for all patients but should be considered on the basis of lipid levels and the presence of other traditional risk factors. Calculation of the 10-year CVD risk using the Systematic Coronary Risk Evaluation (SCORE, https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts) is recommended,[156] although the actual risk is underestimated in patients with SLE.

Certain points to consider and the research agenda suggested by the Task Force Members are reported in box 1. These points aim to improve the design of clinical studies in order to answer clinically important questions, for which the current 'state-of-the-art' is insufficient. In particular, data regarding the optimal duration and timing of discontinuation of therapy in both renal

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Box 1 Future research agenda in SLE

Targets of therapy
- Exploration of a universally accepted level of residual disease activity, if remission cannot be achieved.

Existing therapies and disease monitoring
- Efficacy of calcineurin inhibitor-containing treatment regimens in lupus nephritis (LN) in different racial/ethnic groups and at longer time points.
- Usefulness of measurements of drug blood levels (hydroxychloroquine [HCQ], mycophenolate mofetil and so on).
- Efficacy of quinacrine as immunomodulator in patients with HCQ-induced retinal toxicity.
- Comparative trials of conventional immunosuppressive drugs with global and organ-specific result reporting.
- Randomised trials testing lower cumulative dose glucocorticoid regimens versus conventional regimens.
- Optimal treatment regimen of rituximab: regular versus on-demand.
- Optimal duration of therapy and timing of discontinuation (renal and extrarenal disease).
- Value of repeat kidney biopsy for monitoring LN and determination of clinical versus histological response to therapy.

Pathophysiology and Biomarkers
- Susceptibility to develop systemic lupus erythematosus (SLE).
- Involvement of particular organ systems over others, multisystem versus organ-dominant disease.
- Response to specific therapeutic agents over others (pharmacogenetics, transcriptomics and so on).

Clinical trial design and new drug development
- Optimisation of clinical trial design and study endpoints to maximise probability of new drug approval in SLE.
- Handling of background medication to avoid polypharmacy and 'dilution' of positive effects of drugs under study.
- Inclusion of organ-specific endpoints and disease activity measures.
- Increase in number of adequately trained trial sites (recruitment, infrastructure and training).
- Academia versus industry-driven clinical trials.

and extrarenal disease are scarce;[157] for the former, recent studies support the value of a repeat kidney biopsy for the management of maintenance therapy, but more data are needed.[158 159]

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European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative

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ABSTRACT

Childhood-onset systemic lupus erythematosus (cSLE) is a rare, multisystem and potentially life-threatening autoimmune disorder with significant associated morbidity. Evidence-based guidelines are sparse and management is often based on clinical expertise. SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) was launched to optimise and disseminate management regimens for children and young adults with rheumatic diseases like cSLE. Here, we provide evidence-based recommendations for diagnosis and treatment of cSLE. In view of extent and complexity of cSLE and its various manifestations, recommendations for lupus nephritis and antiphospholipid syndrome will be published separately. Recommendations were generated using the EULAR (European League Against Rheumatism) standard operating procedure. An expert committee consisting of paediatric rheumatologists and representation of paediatric nephrology from across Europe discussed evidence-based recommendations during two consensus meetings. Recommendations were accepted if >80% agreement was reached. A total of 25 recommendations regarding key approaches to diagnosis and treatment of cSLE were made. The recommendations include 11 on diagnosis, 9 on disease monitoring and 5 on general treatment. Topics included: appropriate use of SLE classification criteria, disease activity and damage indices; adequate assessment of autoantibody profiles; secondary macrophage activation syndrome; use of hydroxychloroquine and corticosteroid-sparing regimens; and the importance of addressing poor adherence. Ten recommendations were accepted regarding general diagnostic strategies and treatment indications of neuropsychiatric cSLE. The SHARE recommendations for cSLE and neuropsychiatric manifestations of cSLE have been formulated by an evidence-based consensus process to support uniform, high-quality standards of care for children with cSLE.

INTRODUCTION

Childhood-onset systemic lupus erythematosus (cSLE) is a severe, chronic, systemic autoimmune disease that has great impact on the child or young person affected. cSLE shares its pathogenesis with adult-onset SLE, but generally has a more severe clinical phenotype.[1–8]

With an incidence of 0.3–0.9 per 100 000 children-years and a prevalence ranging from 1.89 to 25.7 per 100 000 children worldwide (reviewed in refs[9–11]), including Europe,[12–16] cSLE fulfils the definition of a rare disease in Europe.[17] Its low prevalence makes clinical research challenging, resulting in a paucity of evidence-based data and subsequent guidelines for disease management. Consequently, the management of patients with cSLE differs widely between countries.[18] Treatment approaches can vary between clinicians even within centres. To foster equity of access to the highest standards of care and uniformity of practice, evidence-based international guidelines are therefore urgently needed.

To achieve this, collaboration between countries is necessary. For this reason, the SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) project was initiated.[18] One of the key objectives of this project was to provide guidance regarding best practices for the diagnosis and management of paediatric rheumatic diseases. SHARE recommendations for autoinflammatory diseases and juvenile dermatomyositis have been published.[19–21] Here, we present SHARE recommendations for cSLE. In view of extent and complexity of cSLE, SHARE recommendations for lupus nephritis (LN) and antiphospholipid syndrome (APS) will be published separately.

METHODS

A European-wide panel of 16 paediatric rheumatologists and representation of paediatric nephrology was established to develop evidence-based recommendations. A project plan for the systematic literature search was written following the EULAR (European League Against Rheumatism) standardised operating procedure.[22] SHARE was a European Union (EU)-funded project and as such there was a prerequisite for representative disease experts from across Europe to form the expert panel, with inclusion of a selected number of disease experts from outside the EU.

Systematic literature search and study selection

A systematic literature search based on specific research questions was performed in PubMed/MEDLINE, EMBASE and Cochrane databases

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in July 2013 (see online supplementary table S1). A validated filter was used to specifically select articles on children and adolescents only.[23] The filter was adapted for cSLE to exclude neonates, as neonatal lupus was beyond the scope of the review (see online supplementary table S2). The literature search also included LN and paediatric APS. These topics will be discussed separately from this article.

Validity assessment

Two reviewers (NG, NdG) independently screened all articles according to the predefined inclusion and exclusion criteria.

Articles were reviewed independently by two cSLE experts from European panel (MWB, SK, TA, AR, IKP, BBM, CP). They assessed level of evidence and methodological quality of the articles (see online supplementary tables S3 and S4).[24 25] Data extraction was done by the experts using predefined data extraction forms adapted from classification tables for epidemiologic, diagnostic[26] and therapeutic[27] studies. If there were any discrepancies, a third expert was asked to give a final assessment.

Establishment of recommendations

The results of the literature review were mapped against the a priori research questions, and provisional recommendations were formulated (NG, NdG, SK, MWB). If no literature in children could be found to map against a particular recommendation, adult literature was consulted. The expert committee (TA, BBM, PB, PD, IKP, PL, LM, SO, CP, AR, AvR, YU, NW, SK, MWB) was presented with the provisional recommendations in web-based surveys (100% response rate) and gave their opinions on the statements. Recommendations were revised according to responses to the surveys and discussed at two sequential face-to-face consensus meetings in March 2014 (Genova, number of experts participating, n=15; moderators: BF and AR) and March 2015 (Barcelona, n=14; moderator: BF).

To reach consensus, the nominal group technique was used, in which equal participation from group members is ensured.[28] Recommendations were accepted when agreement was at least 80%. This process resulted in a final set of prioritised recommendations.

RESULTS

Figure 1 summarises the results of the literature search. A total of 9341 articles were identified and reviewed regarding treatment and management of cSLE, of which 133 articles fulfilled the inclusion criteria. We identified 51 articles relating to diagnosis and management of cSLE generally, and 27 articles to neuropsychiatric manifestations of cSLE, all were scored by the experts (see online supplementary table S1). The 55 articles pertaining to LN informed a specific set of complimentary recommendations that will be published separately.

The meetings resulted in 25 recommendations pertaining to the diagnosis and treatment of cSLE (table 1) and 10 for neuropsychiatric cSLE (NP-cSLE) (table 2). The recommendations in this paper can be used for all patients in whom cSLE is suspected or diagnosed.

The most severe symptom(s) or sign(s) should guide treatment decisions when considering these recommendations. For example, when a patient suffers from mild haematological involvement as well as severe neuropsychiatric disease, the latter should guide the treatment choice.

General diagnostic recommendations

Prompt, accurate diagnosis of cSLE in a specialist centre is crucial to enable timely initiation of appropriate treatment, including multidisciplinary care. However, there are no validated diagnostic criteria for cSLE. Despite some differences regarding symptoms at onset, pattern of organ involvement and severity of disease between cSLE and adult-onset disease,[3 29] their similarities mean that the established American College of Rheumatology (ACR) classification criteria for SLE are widely used for cSLE.[30] In 2012, new classification criteria for SLE were published.[31] To date, two studies have assessed the performance of these Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE in children.[6 7] Both concluded that although some specificity may be lost, the SLICC criteria had better sensitivity than the ACR criteria. Evidence to date indicates the SLICC criteria may well be preferable in cSLE, and should be used to aid referral to, or at least consultation with a paediatric rheumatologist. Similarly, they may help prompt referral, even if a child does not yet meet full criteria, since these are classification and not diagnostic criteria.

A hallmark of SLE is the presence of autoantibodies, particularly those directed towards nuclear autoantigens (antinuclear antibodies, ANA). Next to ANA, autoantibodies including anti-double-stranded DNA (anti-dsDNA), anti-Sm, anti-RNP, anti-Ro/SS-A and anti-La/SS-B (collectively referred to as 'ENA' (extractable nuclear antigens)) are prevalent in cSLE: dsDNA 54%–93%; anti-Sm 17%–52%; anti-RNP 22%–50%; anti-Ro/SS-A 33%–54%; anti-La/SS-B 14%–32%.[5 32–38] As such, including all of these antibodies in the diagnostic work-up when considering cSLE was strongly recommended. However, there are no antibodies with specific predictive qualities (eg, disease severity, organ involvement, age of onset) despite extensive efforts to find them.[39–47] Notably, patients negative for anti-dsDNA antibodies and/or ENA can still be diagnosed with cSLE.

Hereditary complement deficiencies can predispose to lupus or lupus-like disease at an early age. Early recognition of these deficiencies should facilitate adequate treatment of disease and comorbidities including infections, which are especially important as these patients seem to have a higher mortality.[48 49] Therefore, screening for complement deficiencies via CH50, AP50, C3 and C4 (or other validated classic and alternative complement pathway assay) is important in cSLE, especially in young patients with lupus. It was also recognised that there are other causes of monogenic lupus outside of the complement pathway, thus normal complement screening assay results do not preclude this possibility.[50 51]

Cardiopulmonary involvement

Although unusual in cSLE, cardiac and pulmonary involvement does occur, but is often asymptomatic initially.[52–60] Respiratory symptoms or signs such as exertional intolerance could be a sign of pulmonary or cardiac pathology. However, there is a wide differential diagnosis that must be considered and use of appropriate diagnostic procedures should consequently be performed to find out whether cardiopulmonary involvement is due to cSLE.

Early recognition of cardiopulmonary involvement is important when trying to prevent subsequent organ damage. Therefore, a baseline echocardiography and ECG screen in every patient with cSLE for cardiopulmonary involvement is advised. Additionally, intermittent monitoring for any future progression or new involvement of these organ systems over time can be considered, as it is not clear how many children with asymptomatic cardiopulmonary involvement become symptomatic.

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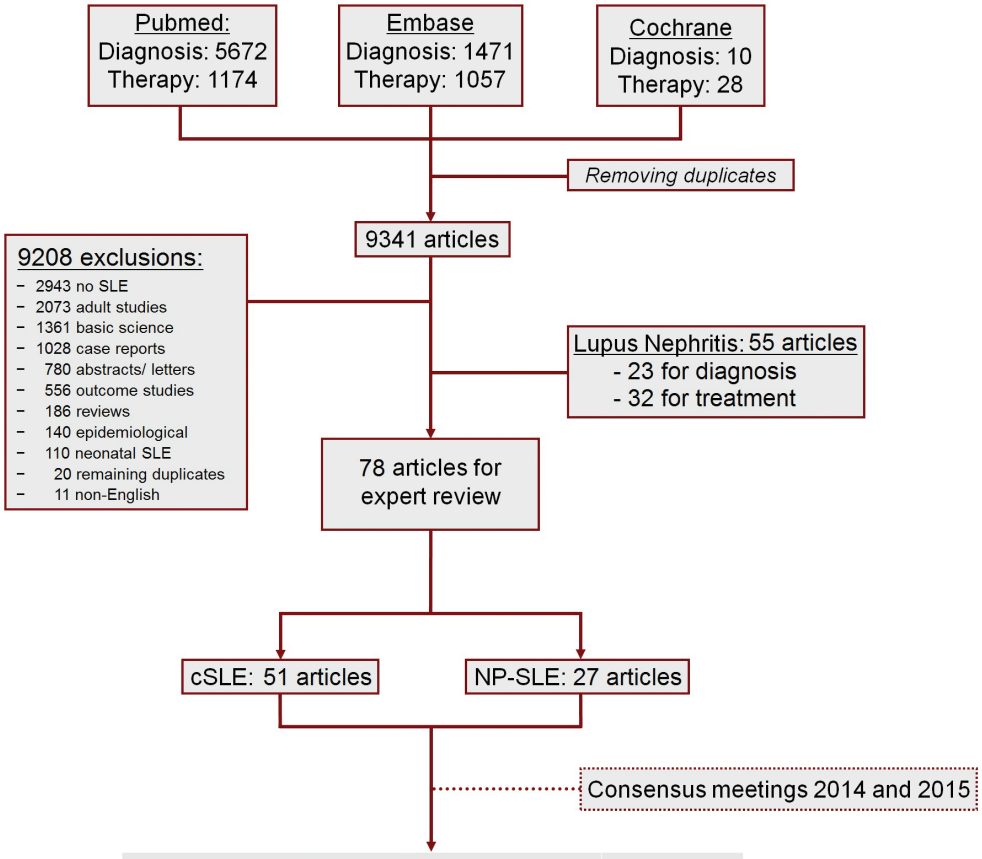

Recommendations regarding:	Number
cSLE	
Diagnosis	11
Management	9
Treatment	5
NP-cSLE	
Diagnosis	6
Management	4

Figure 1 Summary of the literature search. cSLE, childhood-onset systemic lupus erythematosus; LN, lupus nephritis; NP-cSLE, neuropsychiatric cSLE; NP-SLE, neuropsychiatric SLE; SLE, systemic lupus erythematosus.

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a rare but severe, potentially life-threatening complication of cSLE, characterised by high fever, associated in some patients with organ involvement (neurological symptoms, hepatomegaly, splenomegaly), pancytopenia, coagulopathy, elevation of liver enzymes, ferritin and triglycerides.[61 62] Preliminary recommendations for timely diagnosis and correct classification of MAS in cSLE have been developed.[61] Patients can develop MAS at any time during their disease. Distinguishing sepsis from MAS can be difficult, as they may share features such as fever, cytopenias and hepatic involvement, both resulting in systemic inflammation. There are differences, as for example ferritin levels in MAS tend to increase dramatically, whereas hyperferritinaemia is generally more modest in sepsis.[63 64] A bone marrow aspirate should be performed to assess the cause of cytopenias and to detect possible haemophagocytosis. This will help in making a diagnosis of MAS. As MAS can be rapidly progressive and life threatening, the threshold for diagnostic procedures should be low. However, if the patient is clinically unstable, treatment should not be delayed if a bone marrow aspirate is not possible.

Monitoring and general management

The frequency of visits to the paediatric outpatient clinic is dependent on clinical presentation, disease severity as well as the age of the patient. Visits should be regular, especially at diagnosis and following flares and a basic set of investigations is recommended for each visit.[65 66] Consensus was reached on preliminary criteria for global flares in cSLE.[67] Further validation studies are needed to confirm the usefulness of the cSLE flare criteria in research and for clinical care. The recommended frequency of visits as well as the important clinical parameters that should be checked at each visit is similar to the recommendations for adult-onset disease.[68–70] In addition, regular height and weight monitoring is important, as well as pubertal assessment. Growth impairment can occur in children with cSLE, which can be difficult to overcome and may lead to a lower final height due to continuous disease activity and/or corticosteroid use. Similarly, these factors can contribute

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Table 1 Recommendations for cSLE—diagnostic procedures, management and treatment

	Level of evidence	Strength	Agreement (%)
Diagnostic recommendations			
1. Based on the current evidence (mainly in adults) on the SLICC criteria, the SLICC criteria can be used as classification criteria in cSLE.	3	C	100
2. In the presence of a positive ANA combined with at least two clinical SLICC criteria, or in the presence of a positive ANA combined with at least one clinical and one immunological SLICC criterion, referral to a paediatric rheumatologist is warranted.	3	C	100
3. When considering a diagnosis of cSLE, anti-Sm, anti-RNP-a, anti-Ro/SS-A and anti-La/SS-B should be included routinely.	3	C	100
4. In a clinical context, when a patient is ANA positive, but anti-dsDNA and ENA negative, a diagnosis of cSLE can still be made.	3	C	100
5. In patients with cSLE, hereditary complement deficiencies should be considered, especially in young patients.	3	C	100
6. All patients with cSLE should have a chest X-ray at diagnosis.	3	C	100
7. All patients with cSLE should be screened for cardiac abnormalities using ECG and echocardiography at diagnosis.	3	C	100
8. Patients with cSLE with respiratory symptoms or signs (in the absence of acute infection) should have a pulmonary function test including CO diffusion.	3	C	100
9. Exertional intolerance in patients with cSLE should be investigated. Initial investigations should include a chest X-ray, a pulmonary function test (with CO diffusion), echocardiography and an ECG.	3	C	100
10. In patients with cSLE, unexplained fever should trigger a search for infection and MAS.	3	C	93
11. When MAS is suspected, a bone marrow aspirate should be considered to facilitate MAS diagnosis and exclude other diagnoses. If MAS is suspected and the patient is clinically unstable, treatment should not be delayed if a bone marrow aspirate is not possible.	3	C	100
Monitoring and management of cSLE			
1. Active disease should be regularly monitored by performing: a full clinical evaluation including body weight, height and blood pressure; urine dipstick testing; proteinuria estimation; blood tests including albumin; creatinine; eGFR; ESR; C3 and C4; anti-dsDNA; and complete blood cell count.*	2AB/3	B-C/ C	100
2. Clinical evaluation should usually occur every 2–4 weeks for the first 2–4 months after diagnosis or flare, and then according to the response to treatment.*	3	C	100
3. Children receiving systemic corticosteroids should be checked regularly for linear growth.	2A	B	100
4. All children with cSLE should have disease activity assessed regularly using a standardised disease activity measure such as the SLEDAI-2k or pBILAG-2004.	4	D	100
5. All children with cSLE should have disease damage assessed yearly using a standardised disease damage measure such as the paediatric SDI.	3	C	100
6. All patients with cSLE should have access to an ophthalmologist.	3	C	100
7. Annual eye screening should be considered for patients with cSLE taking hydroxychloroquine.	3	C	100
8. Sun protection may be beneficial in patients with skin manifestations and should be considered.*	3	C	100
9. In lupus, a coordinated transition programme including paediatric and adult specialists is crucial for ensuring continuity of care and adherence to treatments in order to optimise long-term outcome including prevention of fatalities.*	3	C	80
Treatment recommendations			
1. All children with lupus should be on hydroxychloroquine routinely.	2A	B	100
2. In all decisions of treatment change or modification, compliance should be actively checked.	3	C	100
3. When it is not possible to taper the prednisone dose, a DMARD should be added to the therapy.	3	C	100
4. Mild/moderate haematological involvement: when haemolysis is present and Hb is lower than normal, a DMARD should be added to the therapy.	3	C	100
5. If rituximab is required, the recommended dose is either 750 mg/m^2/dose (up to a maximum of 1 g) at day 1 and day 15, or 375 mg/m^2/dose once a week for four doses.	3	C	100

*This statement is based on the EULAR recommendations for adults with SLE.[68–70]
Level of evidence: for diagnostic and observational studies: 1A, meta-analysis of cohort studies;1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasiexperimental study; and for treatment studies: 1A, meta-analysis of randomised controlled trial; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion.[22]; Strength of recommendation: A, based on level 1 evidence; 3, descriptive study; 4, expert opinion.[25–27] Agreement indicates per cent of experts agreeing on the recommendation during the final voting round of the consensus meeting.
ANA, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA; CO, carbon monoxide; cSLE, childhood-onset systemic lupus erythematosus; DMARD, disease-modifying antirheumatic drug; eGFR, estimated glomerular filtration rate; ENA, extractable nuclear antigens; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; Hb, haemoglobin; MAS, macrophage activation syndrome; pBILAG-2004, paediatric British Isles Lupus Assessment Group index 2004; SDI, SLICC/American College of Rheumatology Damage Index; SLEDAI-2k, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC, Systemic Lupus International Collaborating Clinics.

to delayed pubertal development. Prepubertal and peripubertal patients receiving a high cumulative dose of corticosteroids are specifically at risk for both growth impairment and pubertal delay, which must be proactively assessed.[71 72]

It is strongly recommended that disease activity, response to treatment and disease damage should be regularly and comprehensively assessed using standardised tools to monitor disease progression. Many tools are available for this purpose.[73–75] For example, disease activity can be monitored with the paediatric

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Table 2 Recommendations for NP-cSLE—diagnostic procedures and treatment

	Level of evidence	Strength	Agreement (%)
Diagnostic recommendations			
1. The nomenclature and case definitions for NP-cSLE syndromes proposed by the ACR ad hoc committee should be used to classify and describe NP-SLE syndromes in cSLE.	3	C	100
2. In patients with cSLE with new or unexplained symptoms or signs suggestive of neuropsychiatric disease, initial diagnostic work-up should include work-up as performed in patients without SLE.	3	C	100
3. In a patient with a suspected diagnosis of NP-cSLE or worsening NP-cSLE symptoms, underlying factors including infections, hypertension, metabolic abnormalities or adverse effects of medication should be excluded.	3	C	100
4. Depending upon the type of neuropsychiatric manifestation, the diagnostic work-up may include lumbar puncture and CSF analysis (primarily to exclude CNS infection), EEG, neuropsychological assessment of cognitive function, consultation with an ophthalmologist, nerve conductional studies and neuroimaging (MRI) to assess nervous system structure and function.*	3	C	100
5. A normal MRI of the CNS does not exclude NP-cSLE.*	3	C	100
6. Cognitive impairment should be tested either in collaboration with a neuropsychologist, or using validated tests for cognitive impairment in cSLE, like the Ped-ANAM.	3	C	100
Treatment recommendations			
1. When neuropsychiatric manifestations are caused by an immune or inflammatory process and non-SLE-related causes are excluded, corticosteroids and immunosuppressive therapy are indicated.	3	C	100
2. Antiepileptic drugs are usually not necessary after a single seizure in the absence of MRI lesions and definite epileptic abnormalities on EEG following recovery from the seizure.*	3	C	100
3. Long-term antiepileptic therapy should be considered for recurrent seizures.*	3	C	93
4. There is a need for paediatric NP-cSLE research regarding treatment.	4	D	100

*This statement is based on the EULAR recommendations for adults with NP-cSLE.[68 123]
Level of evidence: for diagnostic and observational studies: 1A, meta-analysis of cohort studies; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasiexperimental study; and for treatment studies: 1A, meta-analysis of randomised controlled trial; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion.[22] Strength of recommendation: A, based on level 1 evidence; 3, descriptive study; 4, expert opinion.[25–27] Agreement indicates percent of experts agreeing on the recommendation during the final voting round of the consensus meeting.
ACR, American College of Rheumatology; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; EULAR, European League Against Rheumatism; NP-cSLE, neuropsychiatric childhood-onset systemic lupus erythematosus; NP-SLE, neuropsychiatric systemic lupus erythematosus; Ped-ANAM, Pediatric Automated Neuropsychological Assessment Metrics; SLE, systemic lupus erythematosus.

British Isles Lupus Assessment Group index or the Systemic Lupus Erythematosus Disease Activity Index 2000.[73 75–77] Disease damage should also be comprehensively assessed annually, for example using the paediatric version of the SLICC/American College of Rheumatology Damage Index.[71]

A broad range of ocular manifestations including retinopathy or optic nerve disease can occur in cSLE. Additionally, two of the most commonly used drugs for SLE, corticosteroids and hydroxychloroquine (HCQ), can affect the eyes.[78–80] Therefore, it is recommended that patients have access to the expertise of paediatric ophthalmology. Paucity of evidence regarding ophthalmological risks due to long-term corticosteroids and HCQ use means that annual examination of the eyes should be considered in the paediatric age group.[81]

Despite minimal published evidence supporting the benefits of sun protection in patients with cSLE, sunscreens are widely recommended to prevent photosensitive rashes and as part of general disease management. One study in 11 adult patients with SLE showed that some, but not all types of sunscreen prevented the development of ultraviolet radiation-induced skin lesions.[82]

Adolescent patients need to be supported through the transition process and prepared for transfer of their care to the adult services once they reach adulthood. During adolescence, patients need to develop self-management skills and become responsible for their own health.[83–86] One of the major challenges during the transitional process is non-adherence to treatments,[84 87] which should be addressed frequently at outpatient clinics. EULAR recommendations for this transitional process have been published to support professionals in designing a coordinated transition programme.[88]

General treatment recommendations

It is recommended that all children with lupus should be on HCQ routinely. A systematic review of 95 articles analysing the beneficial and adverse effects of antimalarial therapies such as HCQ in adults with SLE showed a broad spectrum of beneficial effects, such as a higher remission rate, less relapses and less accrual of damage. Additionally, HCQ has a favourable safety profile.[89] Adult studies show that long-term use of HCQ is relatively safe, although the risk of retinopathy increases with the increasing cumulative dose.[89] Unfortunately, no such evidence is available for children with cSLE, but studies in patients with juvenile idiopathic arthritis show that doses up to 6 mg/kg/day (based on lean body weight) are safe to use.[90]

Lack of adherence has been associated with a higher disease activity and more damage.[91–93] Rates of non-adherence can be as high as 50% and disease severity does not guarantee medication adherence.[94] Therefore, adherence should be checked whenever a patient shows poor response to a treatment, measuring medication (trough) levels may be helpful to detect non-adherence. When a patient experiences side effects from a drug, choice of therapy will need to be reassessed and switched if necessary. If disease severity is such that tapering of oral prednisolone is not possible despite adequate compliance to oral prednisone and HCQ, addition of a disease-modifying antirheumatic drug (DMARD) is recommended to improve disease control and permit subsequent corticosteroid tapering. Examples of DMARDs often used include mycophenolate mofetil, azathioprine, methotrexate or cyclophosphamide in severe cases.

The use of rituximab has been described in six studies including a total of 115 individual patients with cSLE. All patients had acute, life-threatening symptoms or symptoms that

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did not respond to standard treatment. Two dose regimens were described, which both proved to be effective and safe in the majority of the patients.[95–100]

Diagnostic recommendations

NP-cSLE can be a common manifestation of lupus in children.[101–108] To promote uniformity and comparability between NP-SLE manifestations in children and adults and in view of the limited available evidence in NP-cSLE, it is recommended that the ACR nomenclature and case definitions for NP-SLE[109] are also used in cSLE. It must be taken into account however that the ACR nomenclature was designed for adults and some of the diagnostic or screening tests listed here cannot be used for children. As is the case in adult-onset NP-SLE, no single clinical, laboratory, neuropsychological or imaging test can be used in children to differentiate NP-cSLE from other causes of neuropsychiatric manifestations. There have been some small studies aiming at identification of specific biomarkers or imaging techniques for neuropsychiatric involvement in cSLE, but large controlled studies are lacking.[110–122] Therefore, the recommendation regarding the diagnostic evaluation of neuropsychiatric symptoms is adopted from the adult EULAR recommendations.[68 123]

It is important to make a detailed and thorough assessment of any patient with suspected NP-cSLE. In the context of a suspected NP-cSLE diagnosis or worsening of neuropsychiatric disease, an initial comprehensive work-up should include all other potential underlying causes, including infections, hypertension, metabolic abnormalities or adverse effects of medication. A systematic approach is recommended, with the specific symptoms guiding the type of diagnostic procedure.

Importantly, not all NP-cSLE manifestations can be detected with conventional MRI techniques.[124 125] In addition, conventional MRI techniques (as well as novel MRI imaging modalities) may be unspecific for central nervous system involvement due to cSLE or to other causes. Formal neuropsychiatric testing by a neuropsychologist can be used to ascertain the presence of neurocognitive dysfunction. However, as a neuropsychologist is not always available, a helpful screening tool is the Pediatric Automated Neuropsychological Assessment Metrics, which can be used by non-specialists to screen patients for possible neurocognitive dysfunction[126 127]

Treatment recommendations

The evidence for the treatment of NP-cSLE in children is especially limited. Recommendations are therefore based principally on adult recommendations for the management of NP-SLE,[123] adapted for use in children by the expert panel. It was noted that this remains an important area for future clinical research. When non-SLE-related causes for neuropsychiatric symptoms or signs are excluded, corticosteroids and immunosuppressive therapy are indicated.[123]

Recurrent seizures in SLE may benefit from antiepileptic treatment. However, one single seizure without evidence for epileptic activity on electroencephalogram in the brain is usually not an indication for antiepileptic treatment. Undertaking a careful evaluation seeking and treating the underlying cause, including anti-inflammatory treatment of potential NP-cSLE, most often suffices to prevent further seizures.

DISCUSSION

A total of 35 recommendations for diagnosis, management and treatment for cSLE (25 recommendations) and NP-cSLE (10 recommendations) have been formulated. All recommendations were accepted with >80% agreement.

These recommendations are intended to help specialists with decisions regarding the general care for patients with cSLE. Notably, recommendations regarding the management of nephritis in cSLE and paediatric APS will be published separately.

It must be noted that good quality evidence regarding diagnosis and treatment in cSLE is limited. Due to lack of robust evidence underpinning some statements, the expert panel refrained from being too specific regarding diagnostic procedures, monitoring intervals or specific drug treatments. This emphasises the need for more research on diagnostic procedures, as well as treatment in this population. International collaboration will be vital, as large cohorts are difficult to achieve.

In conclusion, the SHARE project has resulted in recommendations on diagnosis, management and treatment of cSLE and NP-cSLE, based on best available evidence and expert opinion. These recommendations should facilitate the optimisation of the management of this rare disease.

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Correction notice This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

Contributors MWB and SK are senior authors. NW and BV designed the SHARE initiative. NG and NdG performed the systematic literature review, supervised by MWB and SK. Validity assessment of selected papers was done by MWB, SK, TA, AR, IKP, BBM and CP. Recommendations were formulated by NG, MWB and SK. The expert committee consisted of TA, BBM, PB, PD, IKP, PL, LM, SO, CP, AR, AvR, YU, NW, SK, MWB and SDM; they completed the online surveys and/or participated in the subsequent consensus meetings. NG, NdG, SK and MWB prepared the consensus meetings, and NG and NdG chaired the meetings and took minutes. AR and BF facilitated the consensus procedure using nominal group technique. NG, SK and MWB wrote the manuscript, with contribution and approval of all coauthors.

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EULAR recommendations for the management of antiphospholipid syndrome in adults

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ABSTRACT

The objective was to develop evidence-based recommendations for the management of antiphospholipid syndrome (APS) in adults. Based on evidence from a systematic literature review and expert opinion, overarching principles and recommendations were formulated and voted. High-risk antiphospholipid antibody (aPL) profile is associated with greater risk for thrombotic and obstetric APS. Risk modification includes screening for and management of cardiovascular and venous thrombosis risk factors, patient education about treatment adherence, and lifestyle counselling. Low-dose aspirin (LDA) is recommended for asymptomatic aPL carriers, patients with systemic lupus erythematosus without prior thrombotic or obstetric APS, and non-pregnant women with a history of obstetric APS only, all with high-risk aPL profiles. Patients with APS and first unprovoked venous thrombosis should receive long-term treatment with vitamin K antagonists (VKA) with a target international normalised ratio (INR) of 2–3. In patients with APS with first arterial thrombosis, treatment with VKA with INR 2–3 or INR 3–4 is recommended, considering the individual's bleeding/thrombosis risk. Rivaroxaban should not be used in patients with APS with triple aPL positivity. For patients with recurrent arterial or venous thrombosis despite adequate treatment, addition of LDA, increase of INR target to 3–4 or switch to low molecular weight heparin may be considered. In women with prior obstetric APS, combination treatment with LDA and prophylactic dosage heparin during pregnancy is recommended. In patients with recurrent pregnancy complications, increase of heparin to therapeutic dose, addition of hydroxychloroquine or addition of low-dose prednisolone in the first trimester may be considered. These recommendations aim to guide treatment in adults with APS. High-quality evidence is limited, indicating a need for more research.

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder with a wide range of vascular and obstetric manifestations associated with thrombotic and inflammatory mechanisms orchestrated by antiphospholipid (aPL) antibodies. Common APS clinical features include venous thromboembolism, stroke, recurrent early miscarriages and late pregnancy losses.[1] According to current laboratory criteria for APS, aPL antibodies can be one of three types: lupus anticoagulant, anticardiolipin antibodies or antibeta2 glycoprotein I antibodies. Definite APS, fulfilling at least one clinical and one laboratory criteria of the updated Sapporo classification criteria, can occur in association with other autoimmune diseases, mainly systemic lupus erythematosus (SLE), or in its primary form (primary APS).[1 2] Rarely, a life-threatening form of multiorgan thrombosis, known as catastrophic APS (CAPS), can occur. The presence of aPL in asymptomatic individuals or patients with SLE does not confirm the diagnosis of APS but can be associated with increased risk of thrombosis or pregnancy morbidity, depending on aPL characteristics and coexistence of other risk factors.[3 4] The aPL type, the presence of multiple (double or triple) versus single aPL type, their titre (moderate-high titre vs low) and the persistence of aPL positivity in repeated measurements are defined as the 'aPL profile'. The aPL profile is an important factor determining the risk of thrombotic and obstetric events, and consequently the intensity of treatment.[3 4]

Clinical practice in APS is highly variable, in part because it is a rare disorder, and because knowledge about its diagnosis/classification, clinical spectrum and management is continuously advancing. There is a great heterogeneity among studies on the laboratory and clinical criteria used to define APS and the treatment approaches used over the past four decades. These factors make it often difficult to know the best approach to apply in daily practice. In addition, there is a paucity of high-quality randomised controlled trials (RCTs) in APS because of the difficulties in conducting adequately sized trials in an uncommon disease and using randomised designs among patients with often devastating clinical presentations. The objective of this project was to develop evidence-based recommendations for the prevention and management of adult APS that will help guide practice and improve quality of care and patient outcomes.

METHODS

We followed the updated European League Against Rheumatism (EULAR) standardised operating

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procedure[5] and used the Appraisal of Guidelines for Research & Evaluation II tool.[6] The steering committee included the convenor (MGT), co-convenor (AT), methodologist (MMW) and two physicians (LA, ML) responsible for the systematic literature reviews (SLRs) (both were members of the Emerging EULAR Network -(EMEUNET)). The task force included members from 11 European countries: 12 specialists in rheumatology or internal medicine, 2 obstetricians (RF-O, LR), 2 physicians from vascular medicine/thrombosis centres (VP, DW), 1 healthcare professional (KH), and 2 patient representatives (FM, JK).

The convenor prepared the first task force meeting and the first set of research questions on four major topics: risk stratification and risk modification in asymptomatic aPL-positive patients, primary and secondary thromboprophylaxis in APS, management of obstetric APS, and management of CAPS. The research questions were discussed among the task force members, and a set of 31 research questions was formulated using the PICO format (P, population; I, intervention; C, comparator; O, outcomes) and voted according to the Delphi method at a meeting in December 2017.

The data sources for the SLR were PubMed, Embase and the Cochrane Library, which were searched for relevant English-language published articles from their inceptions through 31 January 2018. We included one RCT published after this date because of the importance of its reported safety results (Trial on Rivaroxaban in Antiphospholipid Syndrome (TRAPS) trial).[7] Search terms were developed with the aid of an experienced librarian, who performed the searches. All titles and abstracts of retrieved articles were first reviewed independently by the two literature reviewers. The full-text articles were then reviewed independently by three persons: one literature reviewer, convenor and methodologist. The data abstraction was performed by the two literature reviewers according to a written protocol and supervised by the methodologist. Data abstraction was then independently double-checked by the convenor and methodologist. Each included article was graded for its methodological quality and assigned to the relevant PICO question by the convenor and methodologist. Data were tabulated and summarised by the methodologist in an evidence report that included summary of findings tables with pooled estimates of effect sizes for studies that directly addressed the population, intervention and comparator of PICO questions. Based on this evidence, a first draft of recommendations on 12 topics was prepared by the convenor and co-convenor. The draft recommendations and evidence report were sent to all task force members for review prior to the second task force meeting.

The second task force meeting, held on 3 September 2018, included the presentation of SLR results, discussions of the first draft of recommendations in four working groups, working group presentations of the edited draft for each topic, and discussion and voting of the text. Incorporating additional discussions on wording changes, the final set of overarching principles and recommendations, including the level of evidence (LoE) and grade of recommendations (GoR) according to the Oxford Centre for Evidence-Based Medicine standards[8] prepared by the methodologist in collaboration with convenors, was sent by the convenor to all task force members, who voted anonymously on the level of agreement (LoA). A rating scale of 0–10 (0: do not agree; 10: fully agree) was used for each recommendation. The manuscript was reviewed and approved by all task force members and the EULAR Executive Committee before submission.

Box 1 Definitions of medium-high antiphospholipid antibody (aPL) titres, and of high-risk and low-risk aPL profile

Medium-high aPL titres.

- Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma present in titres >40 IgG phospholipid (GPL) units or >40 IgM phospholipid (MPL) units, or >the 99th percentile, measured by a standardised ELISA. Antibeta2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma in titre >the 99th percentile, measured by a standardised ELISA.[1]

High-risk aPL profile.

- The presence (in 2 or more occasions at least 12 weeks apart) of lupus anticoagulant (measured according to ISTH guidelines), or of double (any combination of lupus anticoagulant, aCL antibodies or antibeta2 glycoprotein I antibodies) or triple (all three subtypes) aPL positivity, or the presence of persistently high aPL titres.

Low-risk aPL profile.

- Isolated aCL or antibeta2 glycoprotein I antibodies at low-medium titres, particularly if transiently positive.[3]

RESULTS

The SLR yielded 7534 articles and 15 hand-searched articles. After the titles and abstracts review, 670 articles were selected for full-text review. The full-text review yielded 249 articles for data abstraction; 61 were excluded and 188 articles were finally considered to be relevant. A detailed presentation of the results of the SLRs that informed the task force recommendations is published separately and should be reviewed together with this report.[9] Based on the SLR results and expert opinion, 3 overarching principles and 12 recommendations were developed.

Overarching principles

1. Identifying the presence of factors associated with high risk for thrombotic and obstetric events is critical in patient management. A major risk factor is the high-risk aPL profile, including any of the following: the presence of lupus anticoagulant as the aPL subtype most closely related to thrombosis, the presence of double (any combination of lupus anticoagulant, anticardiolipin antibodies or antibeta2 glycoprotein I antibodies) or triple (all three subtypes) aPL positivity, or the presence of persistently high aPL titres,[4 10] as also shown by the aPL score[11] and Global Anti-Phospholipid Syndrome (GAPSS) Score.[12] Definitions of medium-high aPL titres and of high-risk and low-risk aPL profiles are included in box 1. Additional risk factors for clinical events are coexistence of other systemic autoimmune diseases, especially SLE, a history of thrombotic and/or obstetric APS, and the presence of traditional cardiovascular risk factors.[3 4 10]
2. The guidelines for cardiovascular disease (CVD) prevention in the general population should be followed. Screening for and management of venous thrombosis risk factors are also recommended. Heparin at prophylactic dosage, preferably low molecular weight heparin (LMWH), should be used in high-risk situations such as surgery, prolonged immobilisation and the puerperium.
3. All patients treated with vitamin K antagonists (VKA) should receive counselling about treatment adherence, the need for

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close international normalised ratio (INR) monitoring especially in the setting of newly initiated treatment or bridging with heparin, the protocol of perioperative bridging therapy with heparin, and drug and food interactions. Counselling should be provided on the use of contraceptives, pregnancy planning and postmenopausal hormone therapy for all women with APS.[13] Patients should also receive dietary counselling for CVD prevention. Physical activity is encouraged in patients with APS including those on oral anticoagulants.

RECOMMENDATIONS

Table 1 presents the LoE, GoR and LoA for each recommendation. For recommendations with B GoR, we used the statement 'is recommended'. For C and D grades, we mostly used the terms 'may be considered' or 'could be considered', with some exceptions according to experts' judgement about the importance of the intervention. Recommendations that are phrased as 'is recommended' are those that the task force meant, based on the evidence and their experience, should be followed in almost all cases.

Primary thromboprophylaxis in aPL-positive subjects

1.In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with low-dose aspirin (LDA) (75–100 mg daily) is recommended.

Use of LDA for primary prophylaxis is supported by results of a meta-analysis of seven observational studies of 460 asymptomatic aPL carriers that found the risk of first thrombosis to be reduced by half in those who used LDA versus those who did not use LDA.[14] Most patients had high-risk aPL profiles, but few had traditional CVD risk factors. An association of similar magnitude was present in a smaller individual patient meta-analysis derived from these studies.[15] Neither meta-analyses display worrisome variations as the directions were clear. Although evidence was largely from observational studies, the panel recommended the use of LDA for primary prophylaxis in asymptomatic aPL individuals with high-risk profile given the likelihood of benefit and low risk of adverse events of this intervention.

2.In patients with SLE and no history of thrombosis or pregnancy complications:

A. With high-risk aPL profile, prophylactic treatment with LDA is recommended.

B.With low-risk aPL profile, prophylactic treatment with LDA may be considered.

Treatment with LDA for patients with SLE and high-risk aPL profile is supported by a subanalysis of eight studies, mostly observational, in a meta-analysis.[14] In this analysis, risk of first thrombosis was reduced by almost half among patients treated with LDA versus patients not treated, without major bleeding events. In an individual patient analysis, this association was independent of the use of hydroxychloroquine (HCQ), suggesting that LDA offers additional benefit in this patient group.[15] Patients with high-risk aPL profile comprised the majority (but not all) of patients in these studies. Although there was heterogeneity between the studies, the direction of effect was clear. Less evidence is available on the use of LDA in patients with SLE and low-risk aPL profile, but pooled data from two cohort studies indicate that the use of LDA was also associated with a lower risk of thrombosis in this group.[16 17]

3.In non-pregnant women with a history of obstetric APS only (with or without SLE), prophylactic treatment with LDA after adequate risk/benefit evaluation is recommended.

The primary prevention of thrombosis with LDA in women with a history of obstetric APS without SLE was addressed in a meta-analysis including five observational studies.[14] The pooled OR for first thrombosis associated with use of LDA was 0.25 (95% CI 0.10 to 0.62). Studies of women with SLE and prior obstetric APS are scarce, but the protective effect of LDA was supported by three retrospective studies that included a minority of patients with SLE.[18–20] The panel recommended the use of LDA in women with a history of obstetric APS only, according to their thrombosis/bleeding risk (aPL profile, coexistent traditional cardiovascular risk factors, intolerance/contraindication to aspirin).

Secondary thromboprophylaxis in APS

4.In patients with definite APS and first venous thrombosis:

A.Treatment with VKA with a target INR 2–3 is recommended.

In patients with APS and first venous thrombosis, after an initial therapy with unfractionated heparin (UFH) or LMWH and bridging therapy of heparin plus VKA, treatment with VKA with a target INR of 2–3 is recommended. Data from an RCT[21] reporting exclusively on patients with venous events and pooled data from five studies that included a majority with venous events[21–25] showed no additional benefit of a target INR of 3–4 vs INR of 2–3. However, evidence is limited by the frequent failure to achieve the target INR in the high-intensity groups in the RCTs. Data on bleeding were not reported for patients with venous thrombosis specifically. However, although not based on data from these studies, higher level of anticoagulation would be anticipated to also have a higher risk of bleeding.

B.Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events. Direct oral anticoagulants (DOACs) could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, allergy or intolerance to VKA).

Despite the broadening use of DOACs in secondary thrombosis prevention in the general population, there is limited evidence about their effectiveness and safety in APS. In a post-hoc analysis of patients with APS included in three RCTs of dabigatran versus warfarin,[26] and in one RCT of rivaroxaban versus warfarin in patients with venous thrombotic APS,[27] there were no differences in outcomes between treatment with DOACs and VKA for venous thrombosis, but the evidence is limited by small samples, under-representation of high-risk patients with APS and short follow-up. A recent RCT of rivaroxaban versus warfarin in patients with APS with triple aPL positivity was prematurely terminated due to an excess of thromboembolic events (mostly arterial) in the rivaroxaban arm.[7] Accordingly, rivaroxaban should not be used in patients with triple aPL positivity. The panel agreed that DOACs may be considered in patients with difficulty achieving a target INR of 2–3 despite compliance with VKA or who have contraindications to VKA. Switching from treatment with VKA to DOACs due to low adherence to VKA or INR monitoring should be avoided.

C.In patients with unprovoked first venous thrombosis, anticoagulation should be continued longterm.

Use of long-term anticoagulation in patients with APS is supported by two small direct comparison studies (one RCT, one retrospective cohort)[28 29] that showed a lower risk of recurrent venous thrombosis among patients with APS on long-term vs 3–6 months of oral anticoagulation. However, studies did not specify the proportion of patients with unprovoked thrombosis, making this evidence indirect.

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Table 1 EULAR recommendations for the prevention and management of APS in adults

Overarching principles

1. Risk stratification in aPL-positive individuals should include determination of the presence of a high-risk aPL profile (defined as any of the following: multiple aPL positivity, lupus anticoagulant or persistently high aPL titres), history of thrombotic and/or obstetric APS, coexistence of other systemic autoimmune diseases such as SLE, and the presence of traditional cardiovascular risk factors.
2. General measures for aPL-positive individuals should include screening for and strict control of cardiovascular risk factors (smoking cessation; management of hypertension, dyslipidaemia and diabetes; and regular physical activity) in all individuals and particularly those with a high-risk aPL profile, screening for and management of venous thrombosis risk factors, and use of LMWH in high-risk situations such as surgery, hospitalisation, prolonged immobilisation and the puerperium.
3. Patient education and counselling on treatment adherence, INR monitoring in patients treated with VKA, use of perioperative bridging therapy with LMWH for patients on oral anticoagulants, oral contraceptive use, pregnancy and postpartum period, postmenopausal hormone therapy, and lifestyle recommendations (diet, exercise) are important in the management of APS.

Recommendations

Statement, LoE*/GoR†	LoA (0–10)‡
Primary thromboprophylaxis in aPL-positive subjects	
1. In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with LDA (75–100 mg daily) is recommended (2a/B).	9.1 (1.5)
2. In patients with SLE and no history of thrombosis or pregnancy complications: A. With high-risk aPL profile, prophylactic treatment with LDA is recommended (2a/B).	9.5 (0.7)
B. With low-risk aPL profile, prophylactic treatment with LDA may be considered (2b/C).	8.9 (1.7)
3. In non-pregnant women with a history of obstetric APS only (with or without SLE), prophylactic treatment with LDA after adequate risk/benefit evaluation is recommended (2b/B).	9.0 (1.3)
Secondary thromboprophylaxis in APS	
4. In patients with definite APS and first venous thrombosis: A. Treatment with VKA with a target INR 2–3 is recommended (1b/B).	9.9 (0.3)
B. Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events (1b/B). DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, allergy or intolerance to VKA) (5/D).	9.1 (1.3)
C. In patients with unprovoked first venous thrombosis, anticoagulation should be continued long term (2b/B).	9.9 (0.3)
D. In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines (5/D). Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence (5/D).	8.9 (1.4)
5. In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with target INR of 2–3: A. Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing, should be considered (5/D).	9.6 (0.8)
B. If the target INR of 2–3 had been achieved, addition of LDA, increase of INR target to 3–4 or change to LMWH may be considered (4–5/D).	9.4 (0.7)
6. In patients with definite APS and first arterial thrombosis: A. Treatment with VKA is recommended over treatment with LDA only (2b/C).	9.4 (0.8)
B. Treatment with VKA with INR 2–3 or INR 3–4 is recommended, considering the individual's risk of bleeding and recurrent thrombosis (1b/B). Treatment with VKA with INR 2–3 plus LDA may also be considered (4/C).	9.0 (1.3)
C. Rivaroxaban should not be used in patients with triple aPL positivity and arterial events (1b/B). Based on the current evidence, we do not recommend use of DOACs in patients with definite APS and arterial events due to the high risk of recurrent thrombosis (5/D).	9.4 (0.9)
7. In patients with recurrent arterial thrombosis despite adequate treatment with VKA, after evaluating for other potential causes, an increase of INR target to 3–4, addition of LDA or switch to LMWH can be considered (4–5/D).	9.3 (1.1)
Obstetric APS	
8. In women with a high-risk aPL profile but no history of thrombosis or pregnancy complications (with or without SLE), treatment with LDA (75–100 mg daily) during pregnancy should be considered (5/D).	9.3 (1.5)
9. In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE: A. With a history of ≥3 recurrent spontaneous miscarriages <10th week of gestation and in those with a history of fetal loss (≥10th week of gestation), combination treatment with LDA and heparin at prophylactic dosage during pregnancy is recommended (2b/B).	9.6 (0.9)
B. With a history of delivery <34 weeks of gestation due to eclampsia or severe pre-eclampsia or due to recognised features of placental insufficiency, treatment with LDA or LDA and heparin at prophylactic dosage is recommended considering the individual's risk profile (2b/B).	9.5 (0.8)
C. With clinical 'non-criteria' obstetric APS such as a the presence of two recurrent spontaneous miscarriages <10th week of gestation, or delivery ≥34 weeks of gestation due to severe pre-eclampsia or eclampsia, treatment with LDA alone or in combination with heparin might be considered based on the individual's risk profile (4/D).	8.9 (1.7)

Continued

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Table 1 Continued

Recommendations	
D. With obstetric APS treated with prophylactic dose heparin during pregnancy, continuation of heparin at prophylactic dose for 6 weeks after delivery should be considered to reduce the risk of maternal thrombosis (4/C).	9.5 (0.9)
10. In women with 'criteria' obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage, increasing heparin dose to therapeutic dose (5/D) or addition of HCQ (4/D) or low-dose prednisolone in the first trimester (4/D) may be considered. Use of intravenous immunoglobulin might be considered in highly selected cases (5/D).	8.7 (1.7)
11. In women with a history of thrombotic APS, combination treatment of LDA and heparin at therapeutic dosage during pregnancy is recommended (4/C).	9.8 (0.5)
CAPS	
12. A. Prompt treatment of infections by early use of anti-infective medications in all aPL-positive individuals and minimisation of interruptions in anticoagulation or low INR level in patients with thrombotic APS are recommended to help prevent the development of CAPS (4/D).	9.6 (0.7)
B. For first-line treatment of patients with CAPS, combination therapy with glucocorticoids, heparin and plasma exchange or intravenous immunoglobulins is recommended over single agents or other combinations of therapies. Additionally, any triggering factor (eg, infections, gangrene or malignancy) should be treated accordingly (5/D).	9.7 (0.6)
In patients with refractory CAPS, B cell depletion (eg, rituximab) or complement inhibition (eg, eculizumab) therapies may be considered (4/D).	9.2 (1.0)

When there are multiple ratings, these follow the order of corresponding subpart of the recommendation.
*Level of evidence (LoE): 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (and low-quality RCT); 3a: systematic review of case–control studies; 3b: individual case–control study; 4: case series and poor-quality cohort and case–control studies; 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
†Grade of recommendation (GoR): A: consistent level 1 studies; B: consistent level 2 or 3 studies, or extrapolations from level 1 studies; C: level 4 studies or extrapolations from level 2 or 3 studies; D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level.
‡Numbers in column 'LoA' indicate the mean and SD (in parenthesis) of the level of agreement among task force members.
APS, antiphospholipid syndrome; aPL, antiphospholipid antibodies. CAPS, catastrophic APS; DOACs, direct oral anticoagulants;EULAR, European League Against Rheumatism;HCQ, hydroxychloroquine; INR, international normalised ratio; LDA, low-dose aspirin; LMWH, low molecular weight heparin; LoA, level of agreement; RCT, randomised controlled trial; SLE, systemic lupus erythematosus; VKA, vitamin K antagonists;

D.In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines. Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence.

This recommendation was based on expert opinion because we did not identify any studies that directly addressed the question of treatment duration after the initial provoked venous thrombosis. The panel recommended a duration of anticoagulation according to international guidelines for patients without APS[30] because the benefit of long-term anticoagulation in this population is unclear. In patients with repeatedly high-risk aPL profile or those with additional risk factors for thrombosis recurrence, longer anticoagulation may be considered.

5. In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with a target INR of 2–3:

A. Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing, should be considered.

B. If the target INR of 2–3 had been achieved, addition of LDA, increase of INR target to 3–4 or change to LMWH may be considered.

There is limited evidence, mainly from case series, about therapeutic strategies for patients who have recurrent venous thrombosis despite a target INR of 2–3. Evaluation of the intensity of anticoagulation and adherence to treatment, patient counselling, frequent INR monitoring or a self-monitoring programme are important in optimising anticoagulation management. For adherent patients who have a recurrent thrombotic event, the addition of LDA, increase of INR target to 3–4 or switch to LMWH can be considered based on the individual's characteristics and preferences (aspirin intolerance/contraindication, cost and side effects of continuous LMWH use). There is insufficient evidence to determine the relative efficacy and safety of these options in this patient group.

6. In patients with definite APS and first arterial thrombosis:

A.Treatment with VKA is recommended over treatment with LDA only.

The use of VKA over LDA is supported by data from observational studies that showed a lower likelihood of recurrent thrombosis among patients with APS and prior arterial thrombosis (mainly stroke) treated with VKA versus LDA alone.[31 32] An early study in older patients with strokes reported no difference in event recurrences between LDA and warfarin, but aPL was tested only once and was mainly of low titre in this study.[33] These issues make it difficult to apply the latter results to patients of any age who fulfil the laboratory criteria for APS.

B.Treatment with VKA with INR 2–3 or INR 3–4 is recommended, considering the individual's risk of bleeding and recurrent thrombosis. Treatment with VKA with INR 2–3 plus LDA may also be considered.

Patients with APS with arterial thrombosis have a higher risk of recurrence compared with those with venous thrombosis, and a tendency for recurrences in the same vascular (arterial) bed.[34] An earlier SLR including mainly observational studies reported that recurrent events occurred more often in patients with APS treated with VKA with a target INR of 2–3 compared with an INR of 3–4, but outcomes among patients with first arterial thrombosis were not analysed specifically.[35] This review did not compare the target INR 2–3 and INR 3–4 arms within the same study, but disaggregated the arms. Pooled data from two retrospective studies and two RCTs[21–24] showed that there was no statistically significant difference in thrombosis recurrences between treatment with VKA with a target INR of 3–4 and treatment with INR of 2–3 (relative risk (RR) 0.46 (0.06–3.52)). However, these studies included a mixture of patients with

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either venous or arterial thrombosis, and a minority had arterial events. In one trial that provided data specifically on patients with arterial thrombosis, there was no difference in recurrences between those treated to a target INR of 2–3 or INR of 3–4 but without statistical significance (HR 3.1 (0.3–30.0)), although the sample was small and the achievement of a target INR of 3–4 was low.[21] Because of these limitations, the higher intensity INR approach is preferred by some centres. In decision-making, physicians should take into account the individual's risk of recurrent thrombosis and major bleeding, as well as the patient's preferences after discussion. Alternatively, treatment with VKA with a target INR of 2–3 plus LDA is used by some experts, supported by limited data from one retrospective cohort study and one small RCT.[36 37]

C.Rivaroxaban should not be used in patients with triple aPL positivity and arterial events. Based on the current evidence, we do not recommend use of DOACs in patients with definite APS and arterial events due to the high risk of recurrent thrombosis.

According to the results of the TRAPS trial,[7] rivaroxaban should not be used in triple aPL-positive patients with APS. In addition, an ongoing trial of apixaban in APS (Apixaban for the Secondary Prevention of Thromboembolism among patients with the Anti-phosPholipid Syndrome ((ASTRO-APS)) (ClinicalTrials.gov identifier: NCT02295475) was recently modified after evaluation of their initial data to exclude patients with arterial thrombosis. Based on these data and those from case series reporting arterial thrombosis recurrences in patients with APS treated with DOACs, use of DOACs is not currently recommended in patients with definite APS and arterial events.[38] Ongoing clinical trials will help to better define the role of DOACs in APS.

7.In patients with recurrent arterial thrombosis despite adequate treatment with VKA, after evaluating for other potential causes, an increase of INR target to 3–4, addition of LDA or switch to LMWH can be considered.

Evidence on the management of recurrent arterial thrombosis despite VKA treatment is limited. The panel agreed that after evaluating other risk factors for thrombosis (eg, traditional cardiovascular risk factors, cancer, other thrombophilic states) and investigating the adherence to VKA treatment, increase of target INR to 3–4, or INR 2–3 with the addition of LDA, or switching to LMWH may be considered. Adjunctive therapy with antimalarials or statins could also be considered.[4 10 39–41]

Obstetric APS

8.In women with a high-risk aPL profile but no history of thrombosis or pregnancy complications (with or without SLE), treatment with LDA (75–100 mg/day) during pregnancy should be considered.

Data from one placebo-controlled RCT of LDA in six women with SLE[42] and data from three low-quality studies (two RCTs, one retrospective cohort)[43–45] of women without SLE found no difference in the prevalence of live births with use of LDA. However, these studies did not specifically include women with a high-risk aPL profile. The panel agreed that use of LDA should be considered in pregnant women with high-risk aPL profile due to the risk of obstetric and thrombotic complications during pregnancy associated with high-risk aPL profile.

9.In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE:

A.With a history of ≥3 recurrent spontaneous miscarriages<10th week of gestation and in those with a history of fetal loss (≥10th week of gestation), combination treatment with LDA and heparin at prophylactic dosage during pregnancy is recommended.

Pooled data from one RCT including only patients with a history of first trimester losses[46] and eight supporting observational studies[47–54] that did not exclusively study women with early pregnancy losses indicated a higher likelihood of live births with combination treatment with LDA and heparin at prophylactic dosage versus LDA alone. Some experts believe that LDA alone can be also effective. For women with a history of fetal loss, combination treatment with LDA and heparin was associated with a higher likelihood of live birth compared with treatment with LDA alone. However, these studies included women with histories of both early and mid-pregnancy losses.[48–52] LDA should be preferably started prior to conception, and heparin (LMWH or UFH) should be added as soon as pregnancy is confirmed. LMWH is preferred for practical reasons.

B.With a history of delivery <34th week of gestation due to eclampsia or severe pre-eclampsia or due to recognised features of placental insufficiency, treatment with LDA or LDA and heparin at prophylactic dosage is recommended considering the individual's risk profile.

Data from two studies (one RCT, one retrospective cohort)[48 55] showed that the likelihood of live births did not differ between women treated with LDA plus heparin and those treated with LDA alone. Physicians should tailor their treatment approach to the individual's risk assessment including aPL profile and other risk situations (eg, presence of other cardiovascular risk factors or immobility).

C. With clinical 'non-criteria' obstetric APS, treatment with LDA alone or in combination with heparin might be considered based on the individual's risk profile.

The 'non-criteria' obstetric APS manifestations included in our search were the presence of two recurrent spontaneous miscarriages <10th week of gestation or delivery ≥34 weeks of gestation due to severe pre-eclampsia or eclampsia. Because studies combined several types of pregnancy losses without specifying on the proportion of 'non-criteria' APS and due to very limited evidence, this recommendation is mainly based on expert opinion. Because of a potential higher risk for obstetric and/or thrombotic complications during pregnancy in women with a history of clinical 'non-criteria' obstetric APS, the panel agreed that treatment with LDA alone or in combination with heparin might be considered, based on an individual's risk profile (aPL profile, concomitant SLE, prior live births, and additional risk factors for pregnancy loss or thrombosis).

D. With obstetric APS treated with prophylactic dose heparin during pregnancy, continuation of heparin at prophylactic dose for 6 weeks after delivery should be considered to reduce the risk of maternal thrombosis.

No studies directly tested the efficacy of extending treatment with prophylactic heparin after delivery. The panel suggested that in women receiving prophylactic dose heparin during pregnancy, the same dosage of heparin should be continued for 6 weeks after delivery due to an increased risk of thrombosis at puerperium.

10.In women with 'criteria' obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage, increasing heparin dose to therapeutic dose or addition of HCQ or low-dose prednisolone in the first trimester may be considered. Use of intravenous immunoglobulin (IVIG) might be considered in highly selected cases.

The most common practice if the combination of LDA and prophylactic dose heparin fails is to increase the dose of heparin to therapeutic dose, although no supporting evidence exists. Other treatment strategies may include the addition of HCQ or low prednisolone doses in the first trimester. Evidence directly

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supporting these treatment options is based on two small observational studies with limited representativeness.[56 57] Use of IVIG was not associated with a higher proportion of live births compared with conventional treatment in three small observational studies[58–60] that directly addressed this question, although confounding by indication may have occurred. Although the expectation of benefit is small, the panel agreed that IVIG might be considered in highly selected cases when other treatments have failed.

11.In women with a history of thrombotic APS, combination treatment of LDA and heparin at therapeutic dosage during pregnancy is recommended.

In observational studies, treatment with LDA and therapeutic dose heparin was associated with live births in 79% of pregnancies on average.[52 61–64] Because a history of thrombotic APS is associated with increased risk for future thrombotic or obstetric events,[65] treatment with LDA and heparin at therapeutic dosage during pregnancy is recommended. Switching treatment from VKA to therapeutic dose LMWH or UFH is recommended as soon as pregnancy is confirmed, ideally before the sixth week of gestation due to the teratogenic effects of warfarin.[66]

Catastrophic APS

12. The most common precipitating factors for the development of CAPS are anticoagulation discontinuation among patients with prior diagnosis of APS, infections and surgical procedures.[67] Early diagnosis and management of infections and minimisation of discontinuation or low-intensity anticoagulation, especially perioperatively, are recommended.[68] Based on the recently published clinical practice guidelines for CAPS management, combination therapy with glucocorticoids, heparin and plasma exchange or IVIG is recommended over single agents as first-line treatment of patients with CAPS.[69] Concurrent treatment of precipitating factors is also recommended (eg, infections, gangrene or malignancy). For refractory CAPS, B cell depletion (eg, rituximab) or complement inhibition (eg, eculizumab) therapies may be considered based on data from case reports.[69]

DISCUSSION

APS is a complex disorder and its management often involves collaboration among several medical specialties. The aim of these recommendations is to provide guidance to all health professionals involved in patient care, inform patients and support their engagement in shared decision-making, and provide evidence to researchers, funders and policy makers. The task force included members from several professional groups covering different perspectives and also involved two patients who participated actively in both meetings.

The main challenge in developing recommendations for the management of adult APS was the low certainty of evidence. Many studies included patients with a mix of different clinical features and did not provide stratified data for arterial or venous thrombosis separately or for each of various types of obstetric APS. This resulted in only indirect evidence for many of the treatment decisions that were examined. Several meta-analyses also pooled studies of heterogeneous patient groups. A high risk of bias and low power, mostly due to the rarity of the syndrome, were also common in RCTs. Therefore, a significant number of recommendations necessarily relied more, or only, on low-quality evidence or expert opinion. An important consideration for future research would be well-designed observational studies and RCTs of homogeneous patient populations. These studies will hopefully increase the quality of evidence for the currently used treatments and answer questions about controversial issues and new potential therapies (box 2).

The cost and availability of suggested treatments are not a barrier to implementation of these recommendations, with the exception of IVIG and plasmapheresis. However, both treatments were recommended as first-line treatment only in CAPS which occurs in less than 1% of patients, while B cell depletion

Box 2 Research agenda

Risk stratification.

- Better definition of high-risk and low-risk aPL profile. Better delineation of the risk associated with different aPL profiles to allow improved classification of patients in research studies.

Primary thrombosis prevention.

- Impact on thrombosis risk of intensive management of traditional risk factors such as smoking cessation, control of hypertension, dyslipidaemia and sedentary behaviour.
- Evaluation of the role of HCQ for primary thrombosis prevention in subjects with high-risk aPL profile: (1) asymptomatic aPL carriers, (2) patients with a history of obstetric APS without SLE and (3) non-criteria APS manifestations (eg, thrombocytopaenia, heart valve disease and aPL-associated nephropathy).
- Evaluation of the role of statins or coenzyme Q10 for primary thrombosis prevention.

Secondary thrombosis prevention.

- Controlled studies of the efficacy and safety of treatment with VKA with target INR of 3–4 versus combination treatment of VKA with target INR of 2–3 and LDA for patients with a history of first arterial thrombosis.
- Duration of VKA in provoked first venous thrombosis.
- Controlled studies of the efficacy of therapy of VKA alone versus VKA plus HCQ for patients with a history of first arterial thrombosis.
- Controlled studies of the efficacy and safety of targeted therapies (eg, B cell depletion therapy, complement inhibitors, or mammalian target of rapamycin (mTOR) inhibitors) in recurrent arterial thrombotic events despite treatment with VKA with a target INR of 3–4.
- Adjunctive treatment for recurrent arterial thrombosis: HCQ, statins or vitamin D. Evaluation of the role of platelet inhibitors (other than LDA), for example, ADP receptor inhibitors, adenosine reuptake inhibitors and others.
- Discontinuation of VKA treatment in patients who became negative for aPL in repeated measurements.

Obstetric APS.

- Controlled studies of the efficacy and safety of treatment with LDA and heparin versus treatment with LDA, heparin and HCQ in women with a history of recurrent obstetric complications.
- Efficacy of 150 mg daily versus 100 mg daily of aspirin.
- Safety and efficacy of statins in pregnant women with APS who develop pre-eclampsia despite treatment with LDA and heparin.

aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; HCQ, hydroxychloroquine; INR, international normalised ratio; LDA, low-dose aspirin; SLE, systemic lupus erythematosus; VKA, vitamin K antagonist.

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and complement inhibitors may be considered in refractory cases of CAPS. Implementation into clinical practice can be facilitated by the dissemination of the recommendations using online media, by presentations in national and international congresses, development of workshops in meetings of different specialties involved in APS management, or educational lectures for healthcare providers in referral hospitals.

Better understanding of the pathophysiological mechanisms of APS will help to identify new therapeutic targets, and a balance between anticoagulation and immunomodulatory drugs for different APS manifestations. In addition, studies that examine homogeneous patient groups can better evaluate the efficacy and safety of the currently available and new treatments. When sufficient new information will be available, an update of the current recommendations will take place. The task force members believe that these recommendations will help to improve the quality of care in patients with APS and foster future research by highlighting evidence gaps.

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Contributors Full-text review, data abstraction and risk of bias assessments were performed by LA and ML, and independently double-checked by MGT and MMW. MMW supervised the methodology of the SLR and prepared the evidence report. MGT and AT prepared the first draft of recommendations, and all authors have participated in the discussion and formulation of recommendations. MGT supervised the project and drafted the manuscript. All authors reviewed the manuscript and approved its final version.

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OPEN ACCESS

EXTENDED REPORT

EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome

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ABSTRACT

Objectives Develop recommendations for women's health issues and family planning in systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS).

Methods Systematic review of evidence followed by modified Delphi method to compile questions, elicit expert opinions and reach consensus.

Results Family planning should be discussed as early as possible after diagnosis. Most women can have successful pregnancies and measures can be taken to reduce the risks of adverse maternal or fetal outcomes. Risk stratification includes disease activity, autoantibody profile, previous vascular and pregnancy morbidity, hypertension and the use of drugs (emphasis on benefits from hydroxychloroquine and antiplatelets/anticoagulants). Hormonal contraception and menopause replacement therapy can be used in patients with stable/inactive disease and low risk of thrombosis. Fertility preservation with gonadotropin-releasing hormone analogues should be considered prior to the use of alkylating agents. Assisted reproduction techniques can be safely used in patients with stable/inactive disease; patients with positive antiphospholipid antibodies/APS should receive anticoagulation and/or low-dose aspirin. Assessment of disease activity, renal function and serological markers is important for diagnosing disease flares and monitoring for obstetrical adverse outcomes. Fetal monitoring includes Doppler ultrasonography and fetal biometry, particularly in the third trimester, to screen for placental insufficiency and small for gestational age fetuses. Screening for gynaecological malignancies is similar to the general population, with increased vigilance for cervical premalignant lesions if exposed to immunosuppressive drugs. Human papillomavirus immunisation can be used in women with stable/inactive disease.

Conclusions Recommendations for women's health issues in SLE and/or APS were developed using an evidence-based approach followed by expert consensus.

INTRODUCTION

Systemic lupus erythematosus (SLE) and the antiphospholipid syndrome (APS), SLE-associated or primary APS, affect mostly women of childbearing age. Several 'unmet needs' in the management of reproductive and other women's health issues may impact on personal relationships and the decision to have children.[1] Because of earlier recognition of disease and advances in medical treatment, family planning has gained greater importance.[2–4] Concerns include the effect of pregnancy on maternal disease, the impact of disease activity on fetal health and the safety of medications during pregnancy and breast feeding. Assessment of fertility and feasibility of assisted reproduction techniques (ARTs), use of contraception, management of menopause and surveillance against malignancies need to be addressed. We gathered a multidisciplinary panel of experts to develop evidence-based recommendations on the management of family planning and women's health issues in SLE and/or APS.

METHODS

We followed the European League Against Rheumatism (EULAR) standardised operating procedures[5] and the Appraisal of Guidelines Research and Evaluation instrument. Through a Delphi-based approach, the committee selected 12 research questions further edited for systematic literature review (see online supplementary table S1). We searched PubMed using arrays of relevant terms; all English-language publications up to December 2014 were considered. A hand search was also performed in October 2015. Retrieved items were refined based on abstract, full-text content and number of included patients. A detailed presentation of the literature review is given in the online supplementary table S2. Evidence was categorised based on the design and validity of available studies and the strength of the statements was graded (see online supplementary table S3). After rounds of

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Table 1 Recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS)

Statement/recommendation	LoA	
	Mean (SD)	Median (IQR)
1. Preconception counselling and risk stratification 1.1 In women with **SLE**, major risk factors for adverse maternal and fetal outcomes include active/flaring SLE **(1/A)**, especially active nephritis **(1/A)**, history of lupus nephritis **(2/B)** and presence of aPL/APS* **(1/A)**. 1.1.1 Blood pressure monitoring **(2/B)**, use of safe medications to control disease activity (emphasis on HCQ **(2/B)**) and limiting glucocorticoids exposure **(2/B)** are essential measures. 1.2 In women with **APS (primary or SLE-APS)**, risk factors include high-risk aPL profile (lupus anticoagulant, multiple aPL, moderate to high titre aPL) **(1/A),** coexisting SLE **(2/B),** history of vascular/thrombotic APS **(2/B)** and of previous adverse pregnancy complications **(2/B)**. 1.2.1 Blood pressure monitoring **(3/C)** and use of antiplatelet and/or anticoagulant therapy (*rated at statement 9*) are of fundamental importance.	10 (0.2)	10 (0)
2. Contraceptive measures 2.1 Women with SLE should be counselled about the use of effective contraceptive measures (oral contraceptives, subcutaneous implants, IUD), based on their disease activity and thrombotic risk (particularly aPL status). IUD can be offered to all the patients with SLE and/or APS free of any gynaecological contraindication **(1/A)**. 2.2 In patients with stable/inactive SLE and negative aPL, combined hormonal contraceptives can be considered **(1/A)**. In women with positive aPL with or without definite APS, hormonal contraception (with progesterone only) must be carefully weighed against the risk of thrombosis **(2/B)**.	9.9 (0.4)	10 (0)
3. Risk factors for reduced fertility Women with SLE who wish to plan a pregnancy should be counselled about fertility issues, especially the adverse outcomes associated with increasing age and the use of alkylating agents **(1/A)**. Treatment with alkylating agents should be balanced against the risk of ovarian dysfunction.	9.8 (0.4)	10 (0)
4. Preservation of fertility Fertility preservation methods, especially GnRH analogues, should be considered for all menstruating women with SLE who are going to receive alkylating agents **(2/B).**	9.5 (0.7)	10 (1)
5. Assisted reproduction techniques 5.1 Assisted reproduction techniques, such as ovulation induction treatments and in vitro fertilisation protocols, can be safely used in patients with SLE with stable/inactive disease **(3/C)**. 5.2 Patients with positive aPL/APS should receive anticoagulation (at the dosage as would be recommended during pregnancy) and/or low-dose aspirin **(3/D)**.	9.6 (0.6)	10 (1)
6. Predictive biomarkers for maternal disease activity in SLE pregnancy In pregnant women with SLE, assessment of disease activity **(1/A)**—including renal function parameters **(2/B)** and serological markers (serum C3/C4, anti-dsDNA titres) **(2/B)**—is recommended to monitor for obstetrical adverse outcomes and disease flares.	9.9 (0.3)	10 (0)
7. Pregnancy monitoring 7.1 Women with SLE and/or APS should undergo supplementary fetal surveillance with Doppler ultrasonography and biometric parameters, particularly in the third trimester to screen for placental insufficiency and small for gestational age fetuses **(3/D)**. 7.2 Fetal echocardiography is recommended in cases of suspected fetal dysrhythmia or myocarditis, especially in patients with positive anti-Ro/SSA and/or anti-La/SSB antibodies **(2/C)**†.	9.7 (0.5)	10 (1)
8. Drugs for the prevention and management of SLE flares during pregnancy 8.1 HCQ **(1/B)**, oral glucocorticoids, azathioprine, ciclosporin A and tacrolimus **(all 3/C)** can be used to prevent or manage SLE flares during pregnancy. 8.2 Moderate-to-severe flares can be managed with additional strategies, including glucocorticoids intravenous pulse therapy, intravenous immunoglobulin and plasmapheresis **(all 3/C)**. 8.3 Mycophenolic acid, cyclophosphamide, leflunomide and methotrexate should be avoided.	9.7 (0.7)	10 (0)
9. Adjunct treatment during pregnancy 9.1 HCQ is recommended preconceptionally and throughout pregnancy for patients with SLE **(2/B)**. 9.2 Women with SLE at risk of pre-eclampsia (especially those with lupus nephritis or positive aPL) should receive LDA **(2/C).** In women with SLE-associated APS or primary APS, combination treatment with LDA and heparin is recommended to decrease the risk of adverse pregnancy outcomes **(1/A)**. 9.3 Supplementation with calcium, vitamin D and folic acid should be offered as in the general population **(–/D)**. Measuring blood vitamin D levels should be considered after pregnancy is confirmed **(–/D)**.	9.8 (0.4)	10 (0)
10. Menopause and HRT HRT can be used for the management of severe vasomotor menopausal manifestations in SLE women with stable/inactive disease and negative aPL **(1/A)**. The use of HRT in patients with positive aPL should be carefully weighed against the risk of thrombosis and cardiovascular disease **(–/D).**	9.6 (0.6)	10 (1)
11. Screening for malignancies Women with SLE and/or APS should undergo screening for malignancies similar to the general population **(–/D)**. Women with SLE, especially those exposed to immunosuppressive drugs, are at higher risk of cervical premalignant lesions and should be monitored with vigilance **(2/B)**.	9.8 (0.4)	10 (0)
12. HPV vaccination HPV immunisation can be considered in women with SLE and/or APS and stable/inactive disease **(3/D)**.	9.2 (1.6)	10 (1)

For each statement or item, the LoE (range 1–3) and the GoR (range A–D) is given in parentheses (refer to online supplementary table S1). In the right-hand columns, the LoA among experts is reported as mean (SD) and median (IQR) values. A score of 10 represents the highest level of agreement.
*aPL and APS are defined according to the updated international consensus criteria.[6] For aPL assays, please see the footnotes of table 2.
†The substatement on fetal echo in women with SLE/APS and positive anti-Ro/La is rated with LoE=2 (ie, sufficient evidence for the association between anti-Ro/La and congenital heart block) but GoR=C due to lack of strong evidence for the clinical implications of this association, namely for the efficacy of interventions.
anti-dsDNA, anti-double-stranded DNA antibodies; aPL, antiphospholipid antibodies; GnRH, gonadotropin-releasing hormone; GoR, grade of recommendation; HCQ, hydroxychloroquine; HPV, human papillomavirus; HRT, hormone replacement therapy; IUD, intrauterine devices; LDA, low-dose aspirin; LoA, level of agreement; LoE, level of evidence.

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Table 2 Checklist of parameters to be considered for preconception counselling and risk stratification in women with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS)

Disease-related risk factors	Prognostic implications
SLE activity/flares* (in the last 6–12 months or at conception)	Increased risk for (i) maternal disease activity (RR 2.1 for subsequent flare during pregnancy and puerperium);[14] (ii) hypertensive complications (OR 1.8 for PE);[15] (iii) fetal morbidity and mortality (OR 5.7 for pregnancy loss,[16] 3.5 for IUGR[17] 6.5 for preterm delivery)[14 15 17–22]
Lupus nephritis (history or active at conception†)	Strong predictor of poor maternal (RR 9.0 for renal flare during/after pregnancy)[23] and fetal outcome(s) (OR 7.3 for fetal loss and 18.9 for preterm delivery)[24 25]
Serological (serum C3/C4, anti-dsDNA titres) activity	Increased risk for maternal SLE flares during pregnancy (OR 5.3)[14] and pregnancy loss[23 26 27]
Previous adverse pregnancy outcome(s)	APS: increased risk for pregnancy complications[28–30]
History of vascular thrombosis	APS: increased risk (ORs ranging 3.6–12.7) for pregnancy morbidity[31]
SLE diagnosis	APS: increased risk (OR 6.9) for pregnancy morbidity[31 32]
aPL profile‡	SLE: strong predictor of adverse maternal and fetal outcomes,[19 25 27 33 34] especially for patients with persistent moderate-to-high aPL titres, LA and multiple aPL positivity (high-risk aPL profile) APS: high-risk aPL profile correlates with increased risk of maternal vascular thrombotic events during pregnancy (OR 12.1),[35] (pre-)eclampsia (OR 2.3),[36 37] APS-related pregnancy morbidity (OR 9.2),[31] IUGR (OR 4.7),[36] preterm birth[38 39]
Anti-Ro/SSA, anti-La/SSB antibodies	Linked to development of neonatal lupus, including a low risk (0.7–2%) for CHB (especially if moderate-to-high anti-Ro titres);[40–43] weak association with other pregnancy complications[44]
End-stage organ damage and associated comorbidities	[45 46]
General risk factors	[47]
Maternal age	
Arterial hypertension	Increased risk for pregnancy loss (OR 2.4,[33] RR 2.9),[48] preterm birth[18 24 27] and IUGR (OR 6.8)[15]
Diabetes mellitus	[49]
Overweight/obesity	
Thyroid disease	[50]
Nicotine and alcohol use	[28]
Immunisations§	

*Diagnosed by validated SLE activity indices and/or physician judgement.
†Evaluated by renal function tests (serum creatinine, blood urea nitrogen) and urinalysis (proteinuria urine sediment).
‡Includes LA, aCL IgG/IgM, aβ2GPI IgG/IgM. The level of positivity of aCL and aβ2GPI antibodies (low vs medium–high) should be defined according to the single assay's characteristics.
§If negative serology, evaluate whether immunisations can be performed prior to pregnancy (eg, rubella).
aCL, anticardiolipin antibodies; aβ2GPI, anti-β2-GPI antibodies; anti-dsDNA, anti-double-stranded DNA antibodies; aPL, antiphospholipid antibodies; CHB, congenital heart block; IUGR, intrauterine growth restriction; LA, lupus anticoagulant; PE, pre-eclampsia; RR, relative risk.

discussions, the committee arrived at 12 final statements (table 1). Each member rated her/his agreement with each statement.

RESULTS AND DISCUSSION

Scope and overarching principles

These recommendations have been devised with the intention of helping physicians involved in the care of patients with SLE and/or APS and facilitating physician–patient communication. They recognise an implicit need for change in the mindset of health professionals, shifting from *caution against* pregnancy towards *embracement* of pregnancy. Accordingly, family planning should be discussed from the first physician–patient encounter and reinforced thereafter. Health professionals should support the patient and her family in their decisions regarding family planning by discussing individual pregnancy risks. Reports on the long-term follow-up of SLE and/or APS offspring are few,[7–10] showing a reassuring picture on the health conditions of the children, with the exception of some cases of neurodevelopmental alterations[11–13] that need further confirmation before they are linked to maternal disease.

Recommendations

Preconception counselling and risk stratification

Assessment of risk factors for adverse maternal and fetal outcomes in pregnant women with SLE and/or APS is crucial for preconception counselling and implementing appropriate preventive strategies and patient-tailored monitoring plan before and during pregnancy (table 2).

In SLE women (with or without APS), prematurity, pre-eclampsia and eclampsia/Hemolysis, Elevated Liver enzyme levels, Low Platelet count (HELLP) rates approximate 25–35%, 10–15% and 1.0–1.5%, respectively.[19 24 25 44 51 52] In APS women (primary or SLE-related), the respective frequencies approximate 25–35%, 10–20% and 3.0–5.0%.[28 29 53 54]

During pregnancy, risk factors associated with adverse outcomes include active/flaring SLE (OR 12.7 for pre-eclampsia/eclampsia;[55] 19.0 for emergency caesarean section;[56] 3.0 for early fetal loss;[20] 5.5 for preterm delivery),[21 19] active nephritis (OR 5.3 for any adverse maternal outcome),[57] hypertension (OR 4.8–7.3 for pre-eclampsia;[52] relative risk (RR) 1.8 for preterm birth)[22] and use of glucocorticoids, especially at maintenance dose ≥10–20 mg/day of prednisone equivalent (OR 3.5 for preterm birth).[58 59] Discontinuation of hydroxychloroquine (HCQ) is related to an increased risk for SLE exacerbations during pregnancy,[24 33 56] and a single placebo-controlled study has suggested a beneficial effect of HCQ on maternal disease activity during pregnancy.[60]

Contraceptive measures

Women with SLE and/or APS should be counselled about contraception, especially for the prevention of unwanted pregnancies during high disease activity periods and intake of teratogenic drugs. Effective contraceptive measures should be

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discussed with the patient by weighing the individual risk factors, including general (hypertension, obesity, tobacco use, family history of hormonal-dependent cancers)[61] and disease-related risk factors, particularly disease activity and thrombotic risk (emphasis on antiphospholipid antibodies (aPLs)).

The intrauterine device (IUD) can be offered to all patients unless there is a gynaecological contraindication. Copper IUD can be used in any patient, while levonorgestrel-containing IUD should be considered only if the benefits of the released hormone (such as the reduction of excessive menstrual bleeding due to anticoagulation)[62] outweigh the risk of thrombosis.[61]

The safety of the combined (oestrogen plus progestin) and progestin-only pill in SLE patients with inactive or stable active SLE and negative aPL has been demonstrated in randomised controlled trials (RCTs).[63 64] In women with *positive aPL (with or without definite APS)*, contraception with combined hormones (oral pill, vaginal ring, transdermal patch) should be discouraged. In young women with myocardial infarction or ischaemic stroke and positive lupus anticoagulant, the use of the combined pill increased the risk of arterial events compared with non-users.[65] In fully anticoagulated patients carrying a low-risk aPL profile, oestrogens might be considered for persistent gynaecological disorders not otherwise managed. Compounds containing progestin only (pill, subcutaneous depot injections) are suitable for these women, although their use should be weighed against the risk of thrombosis. Progestin-only emergency contraception is not contraindicated in patients with SLE and/or APS.

Risk factors for reduced fertility

Few studies have assessed fertility in women with SLE and/or APS by means of hormonal levels (including the anti-Müllerian hormone) or antral follicle count (examined by ultrasound). There is no concrete evidence that the disease *per se* decreases fertility.[66–69]

However, active disease, especially lupus nephritis, and the use of immunosuppressive drugs may negatively impact on fertility. Alkylating agents such as cyclophosphamide (CYC) may cause menstrual irregularities and premature ovarian failure (POF), which is age- and dosage dependent.[70 71]

Similar to the general population, women with SLE and/or APS should be counselled on fertility issues, especially on the negative impact of increasing age (general tendency to postpone childbearing) and certain lifestyle exposures (tobacco use, alcohol consumption). In non-life-threatening disease, treatment with alkylating agents should be balanced against the risk of ovarian dysfunction; rather, less gonadotoxic regimens should be considered.[72] In the presence of multiple risk factors for impaired fertility, ovarian reserve may be assessed in patients with SLE at a younger age than recommended for the general population.[73]

Fertility preservation

Limited data are available on fertility preservation methods in menstruating women with SLE who require treatment with alkylating agents. Cryopreservation of ovarian tissue or oocytes/embryos are poorly investigated options[74 75] and require specialised centres, which may not be easily accessible.

The most extensively studied method for POF prevention in patients with SLE involves gonadotropin-releasing hormone analogues (GnRH-a), with a good safety and efficacy profile (RR 0.12).[76] GnRH-a have been efficacious in patients with cancer.[77 78] GnRH-a are likely to protect against POF, but there are no data on subsequent pregnancies in patients with SLE. They can cause menopause-like symptoms, which are fully reversible upon discontinuation. A study in childhood-onset patients with SLE aged <21 years suggested that GnRH-a should be administered 22 days before CYC is started or continued.[79] It is nevertheless recommended to start the GnRH-a prior to or concomitantly to initiation of the alkylating agent.

Assisted reproduction techniques

Evidence on the efficacy and safety of ARTs (ovulation induction therapy and in vitro fertilisation) in women with SLE and/or APS comes from observational studies.[80–83] Efficacy in terms of pregnancy rate is comparable with that in the general population (up to 30%). ARTs are generally safe if the patient has quiescent disease and is on appropriate antithrombotic treatment if aPL positive. Although it is challenging to define a single protocol, some general measures for prophylaxis in aPL-positive women undergoing ovarian stimulation can be suggested. The type (low-dose aspirin (LDA); low molecular weight heparin (LMWH)) and dosage (prophylactic vs full anticoagulant) of antithrombotic treatment should be recommended as during pregnancy according to the individual risk profile. LDA should be stopped three days before egg retrieval and resumed the following day. Patients taking LMWH should stop it at least 12 hours prior to the procedure and resume it the very same day as long as there is no bleeding. Patients with positive aPL who are not taking LDA during the ovarian stimulation period should start LDA on the day of the embryo transfer, usually in combination with LMWH (which will be continued during pregnancy).

Ovarian hyperstimulation syndrome can be avoided by milder hormonal stimulation or GnRH antagonist protocol.[84] The use of the 'natural cycle' method is another option, although associated with a lower rate of induced pregnancy. The ART induction protocol should be tailored to the individual patient, balancing the safety and effectiveness of the procedure.

Predictive biomarkers for maternal disease activity in SLE pregnancy

Active SLE during pregnancy, assessed by validated disease activity indices[22 56] and/or physician global assessment,[20] is associated with increased risk for maternal and/or fetal complications (*see also paragraph on Preconception counselling and risk stratification*). Pregnancy-specific SLE activity indices have been developed and validated for their sensitivity in detecting changes in disease activity and diagnosing flares (see online supplementary table S4).[85 86] Physicians should be aware of pregnancy physiological changes that can resemble SLE symptoms and signs.[87] Renal activity correlates with adverse pregnancy outcomes and should be monitored by means of urine protein excretion, urine sediment analysis (glomerular haematuria, urinary casts) and serum creatinine level/glomerular filtration rate.[33 49 52] Serological markers are useful in monitoring SLE activity and in the differentiation between disease exacerbation (declining serum C3/C4 levels (even within the normal range) and/or increasing anti-double stranded DNA titres) and pre-eclampsia.[88 89] Smaller increases in serum C3 levels from pregnancy onset to the second or third trimester[19] as well as serological activity (as defined above) that develops during pregnancy, especially in the context of clinical SLE activity, have been associated with increased risk for pregnancy loss,[19 90] intrauterine growth restriction (IUGR)[91] and preterm birth.[19 48 89 90 92]

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Box 1 Ultrasonographic fetal surveillance recommended for pregnant women with systemic lupus erythematosus and/or antiphospholipid syndrome[43 45–48]

- Routine ultrasonographic screening
  - First trimester (11–14 weeks of gestation).
  - Second trimester (with Doppler, preferably at 20–24 weeks of gestation).
- Supplementary fetal surveillance in the third trimester at monthly intervals
  - Doppler sonography of the umbilical artery, uterine arteries, ductus venosus and middle cerebral artery (particularly in fetuses that have been identified to suffer from early intrauterine growth restriction (IUGR), ie, prior to 34 weeks of gestation).
  - In cases of late IUGR (diagnosed after 34 weeks), reduced abdominal circumference growth velocity and/or a reduced cerebroplacental ratio at Doppler investigation was shown to identify fetuses at higher risk of poor perinatal outcome (Doppler of the umbilical artery alone is insufficient).

Pregnancy monitoring

Pregnant women with SLE and/or APS should follow the local protocols applied to pregnancies at high risk for hypertensive disorders and/or placental insufficiency, adjusting the frequency and modality of fetal surveillance according to the maternal and/or fetal status (box 1). Fetal surveillance based on biometric and Doppler findings during the third trimester, and particularly the distinction between early and late IUGR, helps to better tailor the time of delivery and reduce perinatal morbidity and mortality.[93–97] Umbilical and uterine arteries Doppler sonography at 20–24 weeks has good negative predictive value but modest positive predictive value (especially in the absence of biometric signs of fetal growth restriction later in pregnancy) for placental-associated pregnancy disorders such as pre-eclampsia and IUGR. The mode (vaginal vs caesarean section) and timing of delivery are influenced by maternal (hypertensive disorders, anticoagulation status) as well as fetal conditions during pregnancy.

Fetal echocardiography is indicated if there is suspected fetal dysrhythmia or myocarditis, especially in the context of positive maternal anti-Ro/SSA or anti-La/SSB antibodies. Other tests (electrocardiogram plus Holter monitor, magnetocardiography, gated-pulsed Doppler technique, velocity-based fetal kinetocardiogram) might detect subtle signs of the development of congenital heart block (CHB), but are not currently recommended as standard practice.[98] CHB associated with anti-Ro/SSA and/or anti-La/SSB has 16% recurrence rate in women with a previously affected child; therefore, it is recommended to perform serial fetal echocardiograms weekly from 16 weeks of gestation onwards.[98] Considering the low risk (0.7–2%) for CHB in women with no previous CHB, it is unclear whether intensive monitoring (weekly/biweekly between 16 and 26 weeks of gestation and less frequently afterwards)[98] in the general population of anti-Ro/La-positive women is cost-effective. Moreover, there is no proven efficacy of protocols for the prevention or treatment of complete CHB.[99 100] The efficacy of maternal fluorinated steroids has not been established in large cohorts[101–104] despite initial reports of favourable effects in cases of incomplete CHB, cardiomyopathy, endocardial fibroelastosis and hydrops fetalis.[99] Given the potential of fluorinated steroids for major maternal and fetal side effects, the benefit for fetuses with CHB should be stratified according to the presence of risk factors for adverse outcome.[99] Despite its unproven benefit, the current practice of intensive surveillance for CHB onset in women with positive anti-Ro/SSA and/or anti-La/SSB antibodies and no previous child affected by CHB carries no risk and is well accepted by the mothers.[105]

Drugs for prevention and management of SLE flares during pregnancy

A single randomised, placebo-controlled study[60] as well as non-randomised evidence[24 33 56] supports the beneficial role of HCQ in controlling disease activity and preventing flare-ups during pregnancy. Uncontrolled studies suggest an acceptable benefit/risk ratio of oral glucocorticoids,[22 106] azathioprine[59 107] and calcineurin inhibitors (ciclosporin A, tacrolimus)[108 109] in controlling SLE activity during pregnancy. In moderate-to-severe flares, additional modalities can be considered, such as high-dose glucocorticoids (including pulse intravenous therapy),[110 111] intravenous immunoglobulin[20 22] and plasmapheresis (may be also used in refractory nephrotic syndrome).[112 113] CYC should not be administered during the first trimester of pregnancy due to risk for fetal loss (OR 25.5)[20 114] and should be reserved only for the management of severe, life-threatening or refractory SLE manifestations during the second or third trimester. Available data are not sufficient to evaluate the risk of using belimumab in pregnancy[115] and the drug should not be used unless the benefit outweighs the risk to the fetus. Mycophenolic acid, methotrexate and leflunomide should be avoided due to known or possible teratogenicity.[116] To this end, collaborative groups have developed recommendations for the use of antirheumatic drugs before and during pregnancy and lactation.[111 117 118]

Adjunct treatment during pregnancy

Use of HCQ is recommended in women with SLE preconceptionally and throughout pregnancy.[33 56 60] A beneficial role has also been suggested for APS pregnancies,[119–121] but at present there is insufficient data to recommend its routine use in these patients. HCQ may reduce the odds of CHB occurrence in fetuses exposed to maternal anti-Ro/SSA antibodies, especially in mothers who already had a child with CHB.[40 122]

The protective role of LDA against preterm and severe pre-eclampsia has been established in non-autoimmune patients.[123 124] Accordingly, women with SLE at higher risk of pre-eclampsia including those with lupus nephritis or positive aPL will benefit from LDA, preferably given preconceptionally or no later than gestational week 16.[123 124]

In women with definite obstetric APS, combination treatment with LDA and heparin is recommended to decrease the risk of adverse pregnancy outcomes.[16 125–127] Statistically significant results have been demonstrated only for unfractionated heparin in RCTs. However, LMWH is preferable for practical reasons and has shown comparable efficacy in prospective studies.[128 129] Moreover, patients with positive aPL but with no definite classification of APS will benefit from combination therapy if they are considered at moderate to high risk of maternal and fetal complications (see online supplementary table S5).

In addition, other regimens such as prednisolone 10 mg/day in the first trimester, intravenous immunoglobulin or plasmapheresis can be considered for selected patients with APS (refractory obstetric APS, women with previous thrombosis, particularly previous or new cerebrovascular events, women with triple aPL positivity).[119 130–133]

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Box 2 Points to consider and research agenda

- Reproductive issues are of paramount importance for women with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS) and should be addressed on a regular basis by healthcare providers.
- Preconception counselling and risk stratification are essential for prevention of unwanted complications during pregnancy.
- The use of hormonal contraception or replacement therapy is feasible but must be weighed against the individual risk of thrombosis.
- The preservation of fertility should be mentioned while counselling about lifestyles and considered in the treatment choice. Validated protocols for assisted reproduction techniques in patients with SLE and/or APS are needed.
- Predictive biomarkers for maternal disease activity during SLE pregnancy should be expanded with particular focus on the prediction of pre-eclampsia.
- Pregnancy monitoring in SLE and/or APS women should aim at the identification of placental insufficiency with fetal growth restriction in order to decide the best timing for delivery and reduce the risk of perinatal morbidity and mortality.
- The cost-effectiveness of intensive surveillance with fetal echocardiography in patients with positive anti-Ro/SSA and anti-La/SSB antibodies and no previous child with congenital heart block remains to be established.
- Hydroxychloroquine is beneficial during pregnancy to reduce the risk of SLE flares and of poor obstetrical outcomes. More data are needed to support its benefit in APS pregnancies.
- The benefits of cancer surveillance and prevention of gynaecological malignancies need to be communicated to patients.

As recommended in the general population, supplementation with calcium, vitamin D and folic acid should be offered to patients with SLE and/or APS, with particular consideration to those with low circulating levels of 25-OH vitamin D in the first trimester of gestation and receiving glucocorticoids and/or heparin for their detrimental effects on bone mass.

Menopause and hormone replacement therapy

The efficacy and safety of hormone replacement therapy (HRT) (oestrogen plus progestin) in selected patients with SLE has been illustrated in RCTs.[134–136] Benefit was demonstrated mainly in vasomotor and other hypoestrogenism symptoms. No significantly increased risk of severe lupus exacerbations during 12–24 months of HRT was found, although there was a modest increase in mild-to-moderate flares.[132] There was no increased risk of thrombosis and cardiovascular events, although one of the RCTs included only patients with negative aPL and no previous cardiovascular events[132] and another did not detail the aPL profile.[63] Two cohort studies with long-term follow-up did not report significantly increased risk of cardiovascular events during HRT,[137 138] although limitations in power and design preclude firm conclusions. Consequently, HRT should be reserved for the management of severe and disabling vasomotor menopausal symptoms, preferably in SLE women with stable/inactive disease and negative aPL. In patients with positive aPL, the use of HRT should be carefully weighed against thrombotic and cardiovascular risks. If menopause symptoms necessitate HRT, it seems reasonable to start it as early as possible to gain an added benefit for bone protection.[139] Optimal duration of HRT in patients with SLE and/or APS is not known, but it seems reasonable to recommend it for the shortest possible duration.[140 141]

Screening for malignancies

Women with SLE are not at increased risk of breast, ovarian and endometrial cancer compared with the general population,[142 143] and, therefore, should follow the current population screening protocols for these malignancies. Conversely, women with SLE are at higher risk of cervical dysplasia (but not cervical cancer),[144–147] vagina and vulva cancers,[142 147] likely associated with human papillomavirus (HPV) infection. Women with SLE exposed to immunosuppressive drugs, particularly CYC in a cumulative dose-dependent fashion, are at higher risk of cervical dysplasia.[148–151] The suggested timing for Papanicolaou (PAP) smear examination would be once a year in heavily immunosuppressed patients or according to the local screening programme in low-risk patients. Subgroups of women with SLE (Caucasian, younger age, lower education, high SLE damage) may be at risk for poorer adherence to screening programmes.[152 153]

HPV vaccination

HPV vaccination is currently offered to female and male adolescents for preventing precancerous growths and cancer in the cervix and in the genital area. There are reports of venous thromboembolic events (VTEs) associated with the quadrivalent HPV vaccine. However, of the 31 cases (0.2/100 000 doses vaccine) with documented VTE, 90% had a known risk factor for VTE (APS in two cases).[154]

Prospective studies have demonstrated efficacy and safety of HPV vaccination in patients with SLE,[155 156] although seroconversion rates may be lower in patients receiving steroids and immunosuppressive agents. A few cases of severe SLE flares or abrupt SLE onset after HPV vaccination have been reported.[157–159] In accordance with the EULAR recommendations,[160] we recommend that HPV vaccination be offered to young women with stable/inactive SLE and/or APS, according to local protocols, with particular caution in those with high-risk aPL profile.

The points to consider and the research agenda suggested by the Task Force Members are reported in box 2.

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Update of EULAR recommendations for the treatment of systemic sclerosis

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ABSTRACT

The aim was to update the 2009 European League against Rheumatism (EULAR) recommendations for the treatment of systemic sclerosis (SSc), with attention to new therapeutic questions. Update of the previous treatment recommendations was performed according to EULAR standard operating procedures. The task force consisted of 32 SSc clinical experts from Europe and the USA, 2 patients nominated by the pan-European patient association for SSc (Federation of European Scleroderma Associations (FESCA)), a clinical epidemiologist and 2 research fellows. All centres from the EULAR Scleroderma Trials and Research group were invited to submit and select clinical questions concerning SSc treatment using a Delphi approach. Accordingly, 46 clinical questions addressing 26 different interventions were selected for systematic literature review. The new recommendations were based on the available evidence and developed in a consensus meeting with clinical experts and patients. The procedure resulted in 16 recommendations being developed (instead of 14 in 2009) that address treatment of several SSc-related organ complications: Raynaud's phenomenon (RP), digital ulcers (DUs), pulmonary arterial hypertension (PAH), skin and lung disease, scleroderma renal crisis and gastrointestinal involvement. Compared with the 2009 recommendations, the 2016 recommendations include phosphodiesterase type 5 (PDE-5) inhibitors for the treatment of SSc-related RP and DUs, riociguat, new aspects for endothelin receptor antagonists, prostacyclin analogues and PDE-5 inhibitors for SSc-related PAH. New recommendations regarding the use of fluoxetine for SSc-related RP and haematopoietic stem cell transplantation for selected patients with rapidly progressive SSc were also added. In addition, several comments regarding other treatments addressed in clinical questions and suggestions for the SSc research agenda were formulated. These updated data-derived and consensus-derived recommendations will help rheumatologists to manage patients with SSc in an evidence-based way. These recommendations also give directions for future clinical research in SSc.

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease (CTD), which affects skin, blood vessels, heart, lungs, kidneys, gastrointestinal (GI) tract and musculoskeletal system. Involvement of internal organs results in significant morbidity and mortality of patients with SSc. Because of the clinical complexity and heterogeneity of SSc, it is very challenging to treat this disease.[1] Establishing the first European League against Rheumatism (EULAR) recommendations for the treatment of SSc in 2009 was therefore a milestone for improving care of patients with SSc and they were well received by the international community of scleroderma experts.[2 3] In view of several recent developments regarding treatment of SSc-related internal organ involvement, the need of an update of the 2009 EULAR recommendations has been recognised by the EULAR Scleroderma Trials and Research group (EUSTAR) and acknowledged by the EULAR. Following EULAR standardised operating procedures, an ad hoc expert committee was established by EULAR and EUSTAR.[4 5] As in previous recommendations, the global community of SSc experts cooperating within EUSTAR was involved.[6]

Based on the published evidence and expert opinion, 16 updated recommendations regarding pharmacological treatment of SSc-specific organ involvement were formulated. It should be recognised that the field of management of patients with SSc is larger than pharmacological management alone. Management of SSc also includes (early) diagnosis of the disease, early diagnosis of internal organ involvement, identification of patients at risk of development of new organ complications and deterioration of the disease as well as non-pharmacological treatments, of which most of are beyond the scope of this project. There are also several (potential) drugs, including new promising therapies that might be helpful in management of patients with SSc that could not be included in these evidence-based recommendations due to insufficient data at present. The actual recommendations are aimed to guide pharmacological

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treatment of SSc-specific organ involvement. These recommendations are not meant to replace the physician's clinical judgement or the patient-physician shared decision. They should be viewed in light of the clinician's understanding of the individual patient and the clinician's and patients' judgement of the balance between the efficacy and toxicity of a treatment. Although some treatment-related toxicities are mentioned in the text of the recommendations, it still is the responsibility of the physician to recognise and monitor all possible toxicities/side effects according to the information supplied by the producer and all other available sources.

METHODS

Design

These recommendations are an update of the 2009 EULAR recommendations for treatment of SSc.[2] Evidence for existing recommendations was updated with new evidence published since then, all existing recommendations were newly judged and reformulated if necessary. Existing recommendations could also be removed, for instance, when a certain (class of) drugs was withdrawn from the market. New evidence-based recommendations were added.

Expert panel

An expert panel was established with 32 clinical experts in the field of SSc (29 rheumatologists, 1 dermatologist, 2 paediatric rheumatologists with expertise in juvenile SSc), 2 patients with SSc (KF, JW) and 1 clinical epidemiologist (JF) overall representing 11 countries. The clinical experts had to be internationally recognised as specialists in SSc with several years of experience in diagnosing and treating patients with this disease. The two patient partners were nominated by the pan-European patient association for SSc (FESCA). Potential conflicts of interest were declared by all participants. There was no involvement of third parties in the entire process of making these recommendations.

Selection process of clinical questions

To create a comprehensive list of topics of interest, the clinical experts from all EUSTAR centres were asked by email to contribute clinical questions relevant to the pharmacological treatment of SSc. As a result, 170 clinical questions were provided by experts from 41 EUSTAR centres. These questions were then categorised by drug (class) and aggregated with the clinical questions from 2009; duplicates were removed. The clinical questions were phrased according to the 'PICO' format (Patients, Intervention, Comparator, Outcome). Subsequently, the clinical questions were submitted in a three-round web-based Delphi exercise to members of EUSTAR centres, as previously described.[6] The Delphi exercise was completed until May 2014. For more details regarding the Delphi exercise, please see the online supplement.

The results of the Delphi exercise were presented to the expert panel in a first face-to-face meeting in June 2014. In this meeting the Nominal Group Technique was used, based on the results of the Delphi exercise. Finally, the clinical questions were selected that were subjected to the systematic literature search (see online supplementary table S1).

Systematic literature search

The systematic literature search was performed by two fellows (AK, MB) supervised by a task force member (JA), guided by the clinical epidemiologist (JF). For new clinical questions, the literature search was performed on all articles published between 1966 and, as agreed by the panel, until 30 September 2014 in PubMed, EMBASE, the Cochrane Database for meta-analyses and the Cochrane Controlled Trials Register as well as the 2012 and 2013 EULAR and American College of Rheumatology (ACR) congress abstract archives. For clinical questions already included in the existing recommendations the same strategy was followed, searching from February 2007 to 30 September 2014. A standardised search strategy was used for all clinical questions (see online supplementary table S2). Medical subject heading (MeSH) search (exploded) was used for PubMed and a keyword search was used for 2012–2014 or if the MeSH term was not available. For every clinical question, the publications found were screened for eligibility by reading title and abstract. The reference lists of meta-analyses, reviews or systematic reviews were examined to find additional studies.

For details regarding selection of studies, classifying and evaluation of evidence as well as data extraction, see online supplement material.

Recommendations

The evidence of the individual studies was combined to achieve a recommendation in agreement with the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system.[5 7] Accordingly, an evidence profile and a summary of outcomes table were made for every clinical question by AK or MB. Using these results, a set of draft recommendations were prepared by OK-B, JF, UML, YA and OD. The draft recommendations were sent to the expert panel in advance of the second face-to-face consensus meeting in October 2014. Draft recommendations were presented one-by-one together with the evidence profile and outcome tables, moderated by JF. Based on the nominal group technique, all recommendations were discussed, could be reformulated and a level of evidence was attached, until consensus was reached among all participating experts.

RESULTS

The procedure as described above resulted in 16 recommendations being developed (instead of 14 in 2009). These recommendations address treatment of several SSc-related organ complications: Raynaud's phenomenon (RP), digital ulcers (DUs), pulmonary arterial hypertension (PAH), skin and lung disease, scleroderma renal crisis (SRC) and GI involvement. The final set of recommendations, grouped according to organ systems and the future research agenda are summarised in table 1 and box 1, respectively.

In addition to the main recommendations, the experts decided to formulate, several comments addressing therapeutic modalities in research questions, of which at present neither literature-based evidence nor clinical experience allowed precise recommendations to be made (see online supplementary table S3).

Raynaud's phenomenon in patients with SSc

(1) A meta-analysis of randomised controlled trials (RCTs) on *dihydropyridine-type calcium antagonists* indicates that nifedipine reduces the frequency and severity of Raynaud's phenomenon in patients with SSc (SSc-RP) attacks. A meta-analysis of RCTs indicates that *phosphodiesterase type 5 (PDE-5) inhibitors* reduce the frequency and severity of SSc-RP attacks. Dihydropyridine-type calcium antagonists, usually oral nifedipine, should be considered as first-line therapy for SSc-RP. PDE-5 inhibitors should also be considered in treatment of SSc-RP (*strength of recommendation: A*).

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Table 1 The updated EULAR recommendations for treatment of systemic sclerosis, according to the organ involvement, including strength of the recommendations and the results of internal evaluation within the task force group

Organ involvement	Recommendation	Strength of recommendation	Results of internal evaluation
I. SSc-RP	A meta-analysis of RCTs on *dihydropyridine-type calcium antagonists* indicates that nifedipine reduces the frequency and severity of SSc-RP attacks. A meta-analysis of RCTs indicates that *PDE-5 inhibitors* reduce the frequency and severity of SSc-RP attacks. Dihydropyridine-type calcium antagonists, usually oral nifedipine, should be considered as first-line therapy for SSc-RP. PDE-5 inhibitors should also be considered in treatment of SSc-RP.	A	8.19
	A meta-analysis of RCTs on *prostanoids* indicates that *intravenous iloprost* reduces the frequency and severity of SSc-RP attacks. Intravenous iloprost should be considered for severe SSc-RP. Experts recommend that intravenous iloprost should be used for treatment of SSc-RP attacks after oral therapy.	A	8.29
	One small study indicates that *fluoxetine* might improve SSc-RP attacks. Fluoxetine might be considered in treatment of SSc-RP attacks.	C	6.06
II. Digital ulcers in patients with SSc	Two RCTs indicate that *intravenous iloprost* is efficacious in healing digital ulcers in patients with SSc. Intravenous iloprost should be considered in the treatment of digital ulcers in patients with SSc.	A	8.39
	A meta-analysis of RCTs and results of an independent RCT indicate that *PDE-5 inhibitors* improve healing of digital ulcers in patients with SSc. Moreover, the results of one small RCT indicate that PDE-5 inhibitors may prevent development of new digital ulcers in SSc. PDE-5 inhibitors should be considered in treatment of digital ulcers in patients with SSc.	A	8.03
	Bosentan has confirmed efficacy in two high-quality RCTs to reduce the number of new digital ulcers in patients with SSc. Bosentan should be considered for reduction of the number of new digital ulcers in SSc, especially in patients with multiple digital ulcers despite use of calcium channel blockers, PDE-5 inhibitors or iloprost therapy.	A	8.19
III. SSc-PAH	Based on the results of high-quality RCTs including heterogeneous population of patients with PAH, including CTD-PAH, *several ERA* (ambrisentan, bosentan and macitentan), *PDE-5 inhibitors* (sildenafil, tadalafil) and *riociguat* have been approved for treatment of PAH associated with CTDs. ERA, PDE-5 inhibitors or riociguat should be considered to treat SSc-related PAH.	B	8.32
	One high-quality RCT in patients with SSc indicates that continuous *intravenous epoprostenol* improves exercise capacity, functional class and haemodynamic measures in SSc-PAH. Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-PAH (class III and IV).	A	8.10
	Based on the results of high-quality RCTs including heterogeneous population of patients with PAH, including CTD-PAH, *other prostacyclin analogues (iloprost, treprostinil)* have also been registered for treatment of PAH associated with CTDs. Prostacyclin analogues should be considered for the treatment of patients with SSc-PAH.	B	
IV. Skin and lung disease	Two RCTs and their re-analysis have shown that *methotrexate* improves skin score in early diffuse SSc. Positive effects on other organ manifestations have not been established. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc.	A	7.42
	In view of the results from two high-quality RCTs and despite its known toxicity, *cyclophosphamide* should be considered for treatment of SSc-ILD, in particular for patients with SSc with progressive ILD.	A	7.84
	Regarding *HSCT*, two RCTs have shown improvement of skin involvement and stabilisation of lung function in patients with SSc and one large RCT reports improvement in event-free survival in patients with SSc as compared with cyclophosphamide in both trials. HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure. In view of the high risk of treatment-related side effects and of early treatment-related mortality, careful selection of patients with SSc for this kind of treatment and the experience of the medical team are of key importance.	A	8.03
V. SRC	Several cohort studies showed benefit in survival with use of *ACE inhibitors* in patients with SRC. Experts recommend immediate use of ACE inhibitors in the treatment of SRC.	C	8.52
	Several retrospective studies suggest that *glucocorticoids* are associated with a higher risk of SRC. Blood pressure and renal function should be carefully monitored in patients with SSc treated with glucocorticoids.	C	8.10
VI. SSc-related gastrointestinal disease	Despite the lack of large, specific RCT, experts recommend that *PPI* should be used for the treatment of SSc-related GERD and prevention of oesophageal ulcers and strictures	B	8.58
	Despite the lack of RCTs in patients with SSc, experts recommend that *prokinetic drugs* should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction, etc).	C	7.97
	Despite the lack of RCTs in patients with SSc, the experts recommend the use of intermittent or rotating *antibiotics* to treat symptomatic small intestine bacterial overgrowth in patients with SSc.	D	8.10

CTD, connective tissue disease; ERA, endothelin receptor antagonists; EULAR, European League against Rheumatism; GERD, gastro-oesophageal reflux disease; HSCT, haematopoietic stem cell transplantation; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5; PPI, proton pump inhibitor; RCTs, randomised controlled trials; SRC, scleroderma renal crisis; SSc, systemic sclerosis; SSc-RP, Raynaud's phenomenon in patients with SSc.

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Box 1 Research agenda

1. Evaluation of the efficacy and safety of cyclophosphamide in the treatment of early diffuse SSc
2. Evaluation of the efficacy and safety of mycophenolate mofetil and azathioprine in the treatment of SSc
3. Evaluation of the efficacy and safety of anti-CD20 therapies in the treatment of SSc
4. Evaluation of calcium antagonists in the prevention of SSc-PAH
5. Evaluation of calcium antagonists in the treatment of digital ulcers in SSc
6. Evaluation of statins in the treatment of digital ulcers in SSc
7. Evaluation of the efficacy and safety of ACE inhibitors in the prevention of SRC
8. Evaluation of the efficacy of non-pharmacological treatments in SSc

PAH, pulmonary arterial hypertension; SRC, scleroderma renal crisis; SSc, systemic sclerosis.

One meta-analysis, including 8 RCTs: 7 with nifedipine and 1 with nicardipine, with 109 patients with SSc involved, indicated that dihydropyridine-type calcium antagonists reduce the frequency and severity of ischaemic attacks in SSc-RP.[8–15] The weighted mean difference (WMD) of all calcium antagonists versus placebo (six trials) for the reduction in the number of ischaemic attacks over a 2-week period was −8.31 (95% CI −15.71 to −0.91). When the five RCT evaluating nifedipine (10–20 mg three times a day) versus placebo were analysed separately, the reduction was greater with a WMD of −10.21 (95% CI −20.09 to −0.34).

None of the studies included into meta-analysis has directly examined the side effects of calcium antagonists in SSc. Hypotension, dizziness, flushing, dependent oedema and headaches are believed to be fairly common side effects of these agents.[8]

Another meta-analysis of 6 RCTs (2 with sildenafil, 3 with tadalafil and 1 with vardenafil) including 236 patients with connective tissue disease (CTD)-related RP, of whom 95% were patients with SSc, showed that PDE-5 inhibitors improve frequency, severity and duration of RP attacks.[16–22] The treatment effect (mean difference; 95% CI) for daily frequency (−0.49; −0.71 to −0.28), severity (−0.46; −0.74 to −0.17) and daily duration of RP (−14.62; −20.25 to −9.00 min) although significant, was only moderate.

Side effects associated with usage of PDE-5 inhibitors were common and included different forms of vasomotor reactions, myalgias, allergic reaction, chest pain, dyspepsia, nasal stuffiness and visual abnormalities.

Considering long-term experience and good safety profile, *the experts recommend that calcium channel blockers should be used as first-line therapy for SSc-RP and PDE-5 inhibitors in patients with SSc with severe RP and/or those who do not satisfactorily respond to calcium channel blockers*.

(2) A meta-analysis of RCTs on *prostanoids* indicates that *intravenous iloprost* reduces the frequency and severity of SSc-RP attacks. Intravenous iloprost should be considered for severe SSc-RP (*strength of recommendation: A*).

The experts recommend that intravenous iloprost should be used for treatment of SSc-RP attacks after oral therapy.

One meta-analysis, including five RCTs with intravenous iloprost, one RCT with oral iloprost and one RCT with oral cisaprost, with 332 patients with SSc in total, indicates that iloprost is effective in reducing the frequency and severity of SSc-RP.[23–30] Iloprost, given intravenously (0.5–3 ng/kg/min for 3–5 consecutive days sequentially) or orally (50–150 µg twice a day) significantly reduced the frequency of ischaemic attacks, and improved the RP severity score in comparison with placebo (WMD; 95% CI −17.46; −19.19 to −15.73 and −0.69; −1.12 to −0.26, respectively). Oral prostanoids seem to be generally less effective than intravenous iloprost in the treatment of SSc-RP, although some beneficial effects could be seen with higher doses.[29–33]

Two RCTs comparing intravenous iloprost (0.5–2 ng/kg/min for 3–5 days, every 6–8 weeks) with nifedipine (30–60 mg/day) indicate that iloprost is only slightly superior to nifedipine in improving symptoms of SSc-RP.[13 34]

In view of costs and feasibility, *the experts recommended that intravenous prostanoids are considered when oral therapies (including calcium channel blockers and PDE-5 inhibitors) have failed*. As most drugs used for treating RP may induce vascular side effects, *the experts recommend particular attention if prostanoids are combined with other vasodilators*.

(3) One small study indicates that *fluoxetine* might improve SSc-RP attacks. Fluoxetine might be considered in treatment of SSc-RP attacks (*strength of recommendation: C*).

One small study including subgroup analysis of 27 patients with SSc-related RP indicates that fluoxetine (20 mg/day orally) was superior to nifedipine LA (40 mg/day orally) in reduction of severity of RP and comparable with nifedipine in reduction of frequency of RP attacks in patients with SSc.[35] The latter effect was not significant in patients with SSc neither for fluoxetine nor for nifedipine, which could be due to the low number of patients with SSc included. Safety results, available for the combined group of patients with primary RP (n=26) and SSc-related RP (n=27), indicated that fluoxetine was better tolerated than nifedipine: withdrawals due to adverse effects were more than twice higher in the nifedipine group as compared with fluoxetine. Main reasons leading to treatment withdrawals in the fluoxetine group were: apathy, lethargy and impaired concentration.

Despite the relatively low quality of published evidence, *the experts recognise that fluoxetine is used in practice and believe that fluoxetine is a useful alternative for treatment of SSc-RP*, in particular in patients with SSc who cannot tolerate or do not respond to vasodilators.

Since the data regarding the use of fluoxetine in patients with SSc are limited and fluoxetine, as a serotonin-specific reuptake inhibitor and antidepressant, may have potential effects on the central nervous system or heart, it is important to consider potential contraindications before starting treatment and to carefully monitor patients for side effects when on fluoxetine, in particular during long-term treatment.[36] Of note, withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt.

Digital ulcers in patients with SSc

(4) Two RCTs indicate that *intravenous iloprost* is efficacious in healing DUs in patients with SSc. Intravenous iloprost should be considered in the treatment of DUs in patients with SSc (*strength of recommendation: A*).

Intravenous iloprost (0.5–2 ng/kg/min for 3–5 consecutive days) significantly reduced the number of DUs in comparison with placebo in one small RCT (Jadad score 3), and improved DUs healing in another RCT (Jadad score 4) including 73 patients with SSc with active DUs (p=0.06 vs placebo for 50%

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improvement).[27 28] In addition, two RCTs comparing intravenous iloprost with oral nifedipine suggest that both medications have a beneficial effect on DUs, but the number of patients with DUs in both trials was small.[13 34]

One meta-analysis published in 2013 included, in addition to the two above-mentioned RCTs with intravenous iloprost, two additional RCTs, one with oral iloprost (100 or 200 μg/day vs placebo for 6 weeks) and one with oral treprostinil (slow release up to 16 mg two times a day for 20 weeks).[32 37 38] This analysis revealed a trend towards a beneficial effect of prostanoids over placebo for healing of DUs (the pooled risk ratio (RR); 95% CI) for number of patients with DUs improvement or healing: RR 1.33; 95% CI 0.97 to 1.84; p=0.08.[38] The greatest mean effect was seen with intravenous iloprost (RR 3.00; 95% CI 0.76 to 11.81).

The results of this meta-analysis summarising the effect of four RCTs (two with intravenous iloprost, one with oral iloprost and one with oral beraprost) did not show significant effects of prostanoids for the prevention of new DUs in SSc (RR; 95% CI for number of patients with new DUs: 0.85; 0.68 to 1.08, p=0.19).[38] Again, the greatest effect was seen with intravenous iloprost (RR; 95% CI 1.18; 0.30 to 4.72). When the results of the small study by Wigley *et al*[27] were evaluated separately, they suggest that intravenous iloprost may prevent new DUs in patients with SSc (standardised mean difference (SMD); 95% CI for number of DUs: −0.77; −1.46 to −0.08, p=0.03).[38] Moreover, an RCT with epoprostenol, administered continuously for severe SSc-related PAH (SSc-PAH), revealed a tendency towards a reduction in the number of new DUs (by 50%).

Considering the fact that oral prostanoids showed lower efficacy for treatment of SSc-related RP, as compared with intravenous iloprost (see section on Raynaud's phenomenon), *the experts decided*, based on the results of the above-mentioned two RCTs, *to recommend intravenous iloprost as a treatment for DUs in patients with SSc*. Further studies are required to confirm beneficial effect of intraveous iloprost in prevention of development of DUs in patients with SSc. In view of risk of side effects and route of administration usually requiring hospitalisation, intravenous iloprost should be considered in particular in patients with SSc with DUs not responding to oral therapy. In severe cases, combination therapy with oral vasodilator and intravenous iloprost can be used. However, the increased risk of side effects should be taken into account.

(5) A meta-analysis of RCTs and results of an independent RCT indicate that *PDE-5 inhibitors* improve healing of DUs in patients with SSc. Moreover, the results of one small RCT indicate that PDE-5 inhibitors may prevent development of new DUs in SSc. PDE-5 inhibitors should be considered in the treatment of DUs in patients with SSc (*strength of recommendation: A*).

One meta-analysis of three RCTs investigating various selective PDE-5 inhibitors (sildenafil 50 mg twice daily, modified-release sildenafil 100 mg/day increased up to 200 mg/day or tadalafil 20 mg on alternate days) in patients with SSc-RP of whom 39 had baseline DUs indicated that selective PDE-5 inhibitors improved healing of DUs in patients with SSc.[38] Although DUs healing was a co-primary outcome only in one of three RCTs included into the meta-analysis, and all three RCTs were underpowered to detect difference between active treatment and placebo, the pooled effect shows significant benefit of PDE-5 inhibitors over placebo on DUs healing.[18 38] Both the number of patients with DUs healing and the number of patients with DUs improvement were significantly higher for PDE-5 inhibitors as compared with placebo (RR; 95% CI) 3.28; 1.32 to 8.13, p<0.01 for DUs healing and 4.29; 1.73 to 10.66, p<0.002 for DUs improvement, respectively).[38] The results of this meta-analysis are corroborated by an independent multicentre RCT evaluating the effect of tadalafil (20 mg/day on alternate day for 8 weeks as an add-on therapy to previous vasodilators) on DUs healing, as one of two co-primary end points together with effect on RP, in 31 patients with SSc with baseline DUs.[21] After 8 weeks of treatment, DUs healed completely in 14 out of 18 patients in the tadalafil group as compared with 5 out of 13 patients in the placebo arm (p<0.05). The results of this study including altogether 53 patients with SSc-RP indicate that tadalafil was also associated with significantly lower risk of new DUs: new DUs developed in 1 out of 27 patients from the tadalafil group as compared with 9 out of 26 patients from the placebo group (p<0.05). Tadalafil (20 mg/day on alternate day for 6 weeks with 1-week washout period, as add-on therapy to previous vasodilators) prevented development of new DUs in another single-centre cross-over RCT including 24 patients with SSc with secondary RP, 23 (95%) of whom had SSc, cited in the meta-analysis by Tingey *et al*.[20 38] In this study, only 1 new DU developed under tadalafil treatment as compared with 13 new DUs that developed in 6 patients under placebo treatment (p<0.05).

Side effects of PDE-5 inhibitors are discussed in the comment following recommendation regarding PDE-5 inhibitors in treatment of SS-RP.

Based on these data, the experts concluded that PDE-5 inhibitors can be efficacious in treating SSc-related DUs. Whether other than tadalafil PDE-5 inhibitors can prevent development of new DUs in patients with SSc needs to be clarified in further studies.

Annotation: The recently published Sildenafil Effect on Digital Ulcer Healing in sClerodErma (SEDUCE) trial did not reach statistical significance with respect to the influence of sildenafil (20 mg three times daily for 12 weeks) on time to DUs healing, in part due to unexpectedly high healing rates in the placebo group.[39] The study did show significant reduction in the number of DUs per patient at week 8 (1.23±1.61 in sildenafil group vs 1.79±2.40 in placebo group, p=0.04) and week 12 (0.86±1.62 vs 1.51±2.68, p=0.01, respectively) as a result of a greater healing rate. Since *the experts discussed the impact of the study not unambiguously*, and the sildenafil dose used in the SEDUCE study was lower than in the studies included in the above-mentioned meta-analysis by Tingey *et al*,[38] the results of this study, which was published after data closure for the recommendations, did not change the respective recommendation.[39]

(6) *Bosentan* has confirmed efficacy in two high-quality RCTs to reduce the number of new DUs in patients with SSc. Bosentan should be considered for reduction of the number of new DUs in SSc, especially in patients with multiple DUs despite the use of calcium channel blockers, PDE-5 inhibitors or iloprost therapy (*strength of recommendation: A*).

The effect of bosentan, a dual receptor antagonist, on DUs prevention and healing was evaluated in two high-quality RCTs (RAndomized, double-blind, Placebo controlled study with bosentan on healing and prevention of Ischemic Digital ulcers in patients with systemic Sclerosis (RAPIDS)-1 and RAPIDS-2) including altogether 310 patients with SSc with a history of or at least one active DU at baseline. Bosentan, given orally at a dose of 62.5 mg twice a day for 4 weeks followed by 125 mg twice a day for 12 weeks in RAPIDS-1 or 20 weeks in RAPIDS-2, significantly reduced the number of new DUs in both trials.[40 41] In a recent meta-analysis of RAPIDS-1 and RAPIDS-2, treatment with bosentan was associated with a significant reduction in the mean number of new DUs per patient

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in the overall trial population (SMD; 95% CI −0.34; −0.57 to −0.11, p=0.004) and in patients with SSc with baseline DUs (SMD; 95% CI −0.36; −0.61 to −0.11, p=0.005).[38] The effect of bosentan was most pronounced in patients with SSc with multiple (four or more) DUs at baseline (effect size (ES); 95% CI −0.52; −1.01 to −0.02) as compared with patients with SSc with lower number of DUs at baseline (ES; 95% CI −0.08; −0.44 to 0.28) in RAPIDS-2.[41]

The reduction in the number of patients with a new DU was not statistically significant in any of the RAPIDS trials or their meta-analysis.[40 41]

Neither trial indicated that bosentan is superior to placebo in the healing of SSc-related active DUs, as evaluated by the time to complete or partial healing of DUs present at baseline, the time to healing of all DUs or the percentage of patients with complete DUs healing (p>0.05 vs placebo for all comparisons). At present, there is insufficient evidence that endothelin receptor antagonists (ERA) have beneficial effects on SSc-RP attacks either.

There are two major concerns related to the use of bosentan and other ERA: potential liver injury and teratogenicity. Hormonal contraceptives may not be reliable if co-administered with bosentan, because bosentan may reduce their efficacy by interference with the cytochrome P450 system.

In view of the results of both RAPIDS trials and considering potential toxicities associated with bosentan, *the experts recommend usage of bosentan especially in patients who have multiple DUs despite treatment with other vasodilators such as calcium channel blockers, PDE-5 inhibitors and iloprost to prevent the development of new DUs*.

The results of the RAPIDS-2 trial, which were published in full in 2011, did not support the difference in response to bosentan between patients with limited and diffuse SSc subsets, an aspect, which was suggested by the subanalysis of the RAPIDS-1 trial.[40 41] Because of these data, the experts decided that in the present recommendations bosentan should be considered for reduction of new DUs in all patients with SSc with DUs, independent of the disease subset.

Annotation: It should be noted that the effect of bosentan on the prevention of new DUs in SSc has not been proven for other ERA. The results of two double-blind RCTs (Macitentan for the Treatment of Digital Ulcers in Systemic Sclerosis Patients (DUAL)-1 and DUAL-2), which were published after closure of literature research deadline, did not show a significant difference between macitentan, a selective antagonist of ET-1 receptors, and placebo in prevention of new DUs over 16 weeks in patients with SSc with active DUs at baseline.[42]

SSc-related PAH

(7) Based on the results of high-quality RCTs including heterogeneous population of patients with PAH, including CTD-PAH, several *ERA* (ambrisentan, bosentan and macitentan), *PDE-5 inhibitors* (sildenafil, tadalafil) and *riociguat* have been approved for treatment of PAH associated with CTDs. ERA, PDE-5 inhibitors or riociguat should be considered to treat SSc-related PAH (*strength of recommendation: B extrapolation from RCTs including SSc/CTD patients*).

High-quality RCTs involving patients with different forms of PAH, including CTD-related PAH, indicate that endothelin antagonists (bosentan, ambrisentan and macitentan) improve exercise capacity and time to clinical worsening in patients with PAH.[43–45] Adverse events associated with ERA treatment in these clinical trials included abnormal liver function tests, peripheral oedema, palpitations, headache, chest pain, nasal congestion and anaemia, but the safety profile differed for specific agents.[45]

Sitaxentan, a selective ERA which was included in the 2009 EULAR recommendations for the treatment of SSc, has been withdrawn from the market in December 2010 due to its hepatotoxicity.[2 44]

High-quality RCTs involving heterogeneous patients with PAH, including CTD-PAH, indicate that selective PDE-5 inhibitors (sildenafil and tadalafil) improve exercise capacity in patients with PAH and (tadalafil 40 mg/day) reduce risk of clinical worsening.[44 45] The most common side effects associated with PDE-5 inhibitors included flushing, dyspepsia, diarrhoea, headache and myalgia.

Another RCT including patients with different forms of PAH, including patients with CTD-PAH, showed that riociguat, a soluble guanylate cyclase stimulator, improves exercise capacity, time to clinical worsening and haemodynamic parameters in patients with PAH.[46] Drug-related serious adverse events included syncope, increased hepatic enzyme levels, dizziness, acute renal failure and hypotension.[46]

Based on the results of these high-quality RCTs, ERA (bosentan, ambrisentan and macitentan), selective PDE-5 inhibitors (sildenafil and tadalafil) and riociguat have been approved for treatment of PAH associated with CTDs.[44 47 48] The evidence regarding usage of these drugs specifically in SSc-related PAH is less robust.

The experts recommend that ERA, selective PDE-5 inhibitors and riociguat should be considered in the treatment of SSc-related PAH in agreement with international guidelines regarding treatment of PAH.[44] This has been underlined by the publication of the recently published new guidelines of the pulmonology and cardiology societies.[49]

In severe or progressive PAH cases, combination therapy with different PAH-specific drugs should be taken into account. Although at the time of developing these recommendations RCTs comparing combination therapy with PAH-specific drugs versus monotherapy in patients with SSc-PAH were lacking, this approach is in line with recent guidelines of the European cardiology and pulmonology societies regarding management of PAH in general, and seems particularly important in patients with SSc-PAH known to have more progressive disease than patients with other forms of PAH.[49]

(8) One high-quality RCT in patients with SSc indicates that continuous *intravenous epoprostenol* improves exercise capacity, functional class and haemodynamic measures in SSc-PAH. Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-PAH (class III and IV) (*strength of recommendation*: A).

Based on the results of high-quality RCTs including heterogeneous patients with PAH, including CTD-PAH, *other prostacyclin analogues (iloprost, treprostinil)* have also been registered for treatment of PAH associated with CTDs. Prostacyclin analogues should be considered for the treatment of patients with SSc-PAH (*strength of recommendation: B: extrapolation from RCTs including SSc/CTD patients*).

One RCT (Jadad score 3), involving 111 patients with SSc-PAH, showed that epoprostenol (continuous intravenous infusion, starting dose 2 ng/kg/min and increased based on clinical symptoms and tolerability) in combination with conventional therapy (diuretics, oral anticoagulants, oxygen and glycosides), improves exercise capacity, functional status and haemodynamic measures in SSc-PAH, compared with conventional therapy.[50] The median 6 min walk test distance improved by 108 m (95% CI 55 to 180 m; p=0.001; epoprostenol vs control group),

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New York Heart Association functional class improved in 21 (38%) patients treated with epoprostenol and none in the control group (number needed to treat 2.7) and the Borg dyspnoea index and the dyspnoea fatigue score also improved significantly. The beneficial haemodynamic effects of epoprostenol included a statistically significant decrease in pulmonary vascular resistance, mean pulmonary artery pressure and right atrial pressure, as well as a significant increase in cardiac index.[50]

Based on the results of the RCT and two large long-term observational studies, which have documented an improvement in survival of patients with idiopathic PAH treated with epoprostenol, intravenous epoprostenol has been approved by the Food and Drug Administration for the treatment of severe (WHO class III or IV) PAH.[44 45 51 52]

As a result of a very short half-life, epoprostenol is administered through a permanent indwelling central venous catheter, which may incite adverse events: infections, pneumothorax and haemorrhage.[53] Sudden disruption/withdrawal of intravenous epoprostenol (due to catheter/vein thrombosis and/or patient's decision) may lead to life-threatening PAH rebound. *Based on overall risk-to-benefit considerations, and in agreement with the current guidelines, the experts recommend intravenous epoprostenol as the treatment of choice in severe, therapy-resistant SSc-PAH, which are in line with those of recently published guidelines of other societies*.[44 49]

Based on the results of high-quality RCTs involving patients with different forms of PAH, including patients with CTD-PAH, other prostacyclin analogues such as treprostinil (intravenous, subcutaneous or inhaled) and iloprost (inhaled) have been approved for treatment of PAH, including PAH associated with CTD.[44 45] Side effects associated with usage of intravenous treprostinil are similar to that reported with intravenous epoprostenol and include headache, jaw pain, diarrhoea, abdominal pain, anorexia, vomiting, photosensitivity, cutaneous flushing and arthralgias, as well as the risk of complications associated with continuous infusion via catheter. Subcutaneous infusion of prostanoids is frequently associated with pain at the infusion site. Inhaled prostanoids can result in cough, headache, flushing, nausea and syncope.[45]

Despite the lack of specific RCTs evaluating these drugs exclusively in patients with SSc, the experts recommend that these prostacyclin analogues should be considered for treatment of SSc-PAH, in agreement with international guidelines for PAH treatment.[44 49]

The experts concluded that combining different classes of PAH-specific therapies may be considered in the treatment of selected patients with SSc-PAH, especially in those with severe or progressive disease. As discussed in previous paragraph, this approach is in line with recently published guidelines regarding management of PAH in general, and seems particularly important in patients with SSc-PAH known to have more progressive disease than patients with other forms of PAH.[49]

Skin and lung disease

(9) Two RCTs and their re-analysis have shown that *methotrexate* improves skin score in early diffuse SSc. Positive effects on other organ manifestations have not been established. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc (*strength of recommendation: A*).

In one RCT (Jadad score 3), involving 29 patients with diffuse SSc or limited SSc (mean duration of skin involvement 3.2 years), methotrexate (intramuscularly at a dose of 15 mg/week for 24 weeks) showed a trend towards improvement of the total skin score ($p=0.06$ vs placebo).[54]

In the second RCT (Jadad score 5), involving 73 patients with early diffuse SSc, methotrexate, given orally at a dose of 10 mg/week for 12 months, decreased the University of California Los Angeles (UCLA) skin score (ES 0.5, 95% CI 0.0 to 1.0) and the modified Rodnan skin score (mRSS, ES 0.5; 95% CI 0.0 to 0.9) compared with placebo in an intention-to-treat analysis.[55] A beneficial effect of methotrexate (over placebo) on skin manifestations has been confirmed by a re-analysis of the trial by Pope *et al*[55] which, using a Bayesian methodology, showed that the probability that methotrexate improves mRSS and the UCLA skin score were 94% and 96%, respectively.[56] No significant effects on other organ manifestations were shown. In the study evaluating patients with early diffuse SSc, 11 out of 36 patients (31%) in the placebo group and 12 out of 35 patients (34%) in the methotrexate group dropped out before study completion, mainly due to treatment inefficacy. There were few premature discontinuations due to adverse events (number needed to harm 16 and 34.5 in both RCTs, respectively). There were no significant differences in the mortality rate (three vs seven; $p=0.18$), although the trend was in favour of methotrexate.[55] Safety concerns associated with methotrexate include liver toxicity, pancytopenia, its potential teratogenicity and, possibly, the induction of lung injury.[57] It should be noted that in both RCTs evaluating methotrexate in SSc, relatively low dose of methotrexate was used. Whether higher doses of methotrexate, which are used in treatment of rheumatoid arthritis and other inflammatory diseases, could increase treatment effectiveness without significant increase in risk of side effects remains to be established. In paediatric patients, methotrexate dose of 25 mg/m^2/week orally or subcutaneously is well tolerated.

Thus, the experts confirmed the earlier recommendation for methotrexate in early diffuse SSc.

It should be recognised that cyclophosphamide (CYC) has also been shown, in RCTs, to improve skin changes in patients with SSc, and other agents such as mycophenolate mofetil or azathioprine are used to treat skin involvement, although their efficacy has not been studied extensively.[58]

(10) In view of the results from two high-quality RCTs and despite its known toxicity, *cyclophosphamide* should be considered for treatment of SSc-related interstitial lung disease (SSc-ILD), in particular for patients with SSc with progressive ILD (*strength of recommendation: A*).

The evidence regarding efficacy of CYC in SSc-ILD results mainly from two high-quality (Jadad score 5) RCTs and their subanalyses.[58 59] The first trial (Scleroderma Lung Study (SLS)), involving 158 patients with SSc with active alveolitis, demonstrated that CYC given orally at a dose of 1–2 mg/kg/day improved lung volumes, dyspnoea score and quality of life over 12 months compared with placebo.[58] The placebo-corrected mean (95% CI) improvement in forced vital capacity (FVC) and total lung capacity (TLC) was 2.5% (0.3%–4.8%) and 4.1% (0.5%–7.7%), respectively ($p=0.03$ for both measures). No significant effect on diffusing lung capacity for carbon monoxide (DLCO) could be demonstrated. CYC also improved the transitional dyspnoea index, the health assessment questionnaire (HAQ) disability index and the vitality and health-transition domains of the Short-Form 36 ($p<0.05$ vs placebo for all measures).[58] Subanalysis of the SLS revealed that CYC therapy was also associated with significant improvement in high resolution computed tomography (HRCT) score.[60] Extension of the SLS study showed that the FVC continued to improve after cessation of CYC treatment reaching a maximum at 18 months: 6 months after stopping CYC therapy (mean FVC difference vs placebo:

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4,16%, p=0.01).[61] The beneficial effects of CYC disappeared 1 year after CYC was terminated. The effect of CYC was greater in patients with more severe lung and/or skin disease.[61 62] The mean FVC improvement in patients with baseline FVC lower than 70% of predicted was 4.62% at 12 months and 6.8% at 18 months (p<0.006 for both time points), while in patients with baseline FVC>70% of predicted the mean treatment effect was 0.55% at 12 months and 2.67% 18 months (p>0.05 for both time points). Another subanalysis of the SLS study revealed that the HRCT score and skin disease were independent predictors of response to CYC therapy.[62] In patients with 50% or more of any lung zone involved by reticular infiltrates on HRCT and/or with mRSS of at least 23/51, the CYC treatment effect was 9.81% at 18 months (p<0.001) versus no treatment effect (0.58% difference, p>0.05) in patients with less severe HRCT findings and a lower mRSS at baseline.

The second trial evaluated CYC (intravenously at a dose of 600 mg/m^2/month) compared with placebo in 45 patients with SSc-ILD.[59] Active treatment included six infusions of CYC given at 4-week intervals followed by oral azathioprine (2.5 mg/kg/day) or placebo for 6 months. Prednisolone (20 mg on alternate days) was co-administered in the active treatment group. The mean adjusted between-group difference in FVC was 4.2% in favour of CYC, which just missed statistical significance (p=0.08). The lung diffusing capacity for carbon monoxide and other outcome measures did not improve.[59]

Considering the results of both RCTs and the fact that the benefit of CYC was mainly due to inhibition of progression of SSc-ILD, the experts recommend that CYC therapy should be considered in particular in patients with progressive lung disease. As in the previous 2009 recommendations there *was unanimous consensus of the experts with respect to the CYC dose and duration of treatment to be tailored individually dependent on the clinical condition and response*. Potential risks of bone marrow suppression, teratogenicity, gonadal failure and haemorrhagic cystitis must be always considered.[63]

(11) Regarding *haematopoietic stem cell transplantation (HSCT)*, two RCTs have shown improvement of skin involvement and stabilisation of lung function in patients with SSc and one large RCT reports improvement in event-free survival in patients with SSc as compared with CYC in both trials. HSCT should be considered for the treatment of selected patients with rapidly progressive SSc at risk of organ failure. In view of the high risk of treatment-related side effects and of early treatment-related mortality, careful selection of patients with SSc for this kind of treatment and the experience of the medical team are of key importance (*strength of recommendation: A*).

The results of two RCTs evaluating the efficacy and safety of high-dose immunosuppressive therapy with subsequent HSCT have been published so far.[64 65] The first single-centre trial (Jadad 3), including 19 patients with SSc with mRSS >14 and internal organ involvement or mRSS <14 and SSc-ILD, showed that HSCT (200 mg/kg CYC and rabbit antithymocyte globulin 6.5 mg/kg intravenously in total, preceded by CYC 2 g/m^2 and filgastrim as part of the mobilisation step prior to leukapheresis) was superior to CYC (intravenously, 1 g/m^2/month for 6 months) therapy with respect to improvement of skin score and lung volumes.[64] No significant effect on diffusing capacity of the lungs for carbon monoxide could be demonstrated.

Another multicentre RCT (The Autologous Stem Cell Transplantation International Scleroderma (ASTIS)) compared HSCT (200 mg/kg CYC and rabbit antithymocyte globulin 7.5 mg/kg intravenously in total, preceded by CYC 4 g/m^2 and filgrastim as part of the mobilisation step) with CYC pulse therapy (intravenously, 750 mg/m^2/month for 12 months) in 156 patients with SSc with early diffuse SSc, mRSS ≥15 and internal organ involvement or with an mRSS >20 without internal organ involvement.[65] HSCT was associated with increased treatment-related mortality in the first year (eight deaths in HSCT group vs none in CYC group, p=0.007), but significantly improved long-term event-free survival (HR; 95% CI 0.52; 0.28 to 0.96, p=0.04 and 0.34; 0.16 to 0.74, p=0.006 at 1 and 3 through 10-year follow-up) and overall survival (HR; 95% CI 0.48; 0.25 to 0.91, p=0.02 and 0.29; 0.13 to 0.64, p=0.002 at 1 and 3 through 10-year follow-up). HSCT therapy resulted in significant improvement in the mRSS (mean difference; 95% CI 11.1; 7.3 to 15.0, p<0.001), FVC (mean difference; 95% CI 9.1; 14.7 to 2.5, p=0.004) and TLC (mean difference; 95% CI 6.4; 11.9 to 0.9, p=0.02) at 2 years follow-up. No significant effect on DLCO could be found. Mean change in creatinine clearance was significantly worse in the HSCT group than in the control group (mean difference; 95% CI 10.9; 1.5 to 20.3 p=0.02). Causes of treatment-related deaths in HSCT included Epstein-Barr virus reactivation, lymphoma, heart failure, myocardial infarction and acute respiratory distress syndrome. HSCT therapy was also associated with higher risk of viral infections (27.8% in the HSCT group vs 1.3% in the control group, p<0.001).

In view of the results of the two RCTs and considering the risk of potential treatment-related mortality and morbidity, *the experts recommend that HSCT should be considered for the treatment of selected patients with rapidly progressive SSc at risk of organ failure*. To reduce the risk of treatment-related side effects, HSCT should be performed in selected centres with experience in this kind of treatment. Careful evaluation of the benefit to risk ratio in individual patients with SSc selected for HRCT should be done by experts. Further studies should help to identify subgroups of patients with SSc in whom HSCT would be most beneficial.

Scleroderma renal crisis

(12) Several cohort studies showed benefit in survival with use of *ACE inhibitors* in patients with SRC. The experts recommend immediate use of ACE inhibitors in the treatment of SRC (*strength of recommendation: C*).

RCTs evaluating the efficacy of ACE inhibitors in the treatment of SRC are lacking. Since the first report demonstrating a beneficial effect of ACE inhibitors in two patients with SRC, numerous case reports and uncontrolled studies have reported on ACE inhibitors in SRC.[66–72] A prospective analysis of 108 patients with SRC has suggested that patients on ACE inhibitors (captopril in 47 and enalapril in 8) had a significantly better survival rate at 1 year (76%) and 5 years (66%) compared with patients not on ACE inhibitors (15% at 1 year and 10% at 5 years, respectively). The beneficial effect of ACE inhibitors on survival in SRC remained significant after adjustment for age and blood pressure (p=0.001).[68] Another prospective uncontrolled study of 145 patients with SRC treated with ACE inhibitors demonstrated survival rates at 5 and 8 years after the onset of SRC of 90% and 85%, respectively.[69] Two more recent retrospective studies including 91 and 110 patients with SRC respectively, the majority of whom (91% and 98%. respectively) were treated with ACE inhibitors and/or angiotensin receptor antagonists (ARA) reported survival rates from 71% to 82% at 1 year, 59% to 60% at 5 years and 42% to 47% at 10 years.[71 72] In comparison, three out seven (43%) patients without ACE inhibitors/ARA-2 died within the first months after SRC onset.[71]

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It is highly unlikely that a formal RCT will be conducted in this rare condition with high mortality. Despite the lack of RCTs, the experts recommend the use of ACE inhibitors in the treatment of scleroderma renal crisis (SCR). The *experts believe that an immediate start of high-dose ACE inhibitors in patients who develop SRC is of key importance for improving their outcome*. ACE inhibitors should be continued long-term as long as there is any chance for additional improvement in kidney function.

The experts decided also to highlight that published evidence does not support the preventive use of ACE inhibitors to decrease risk of development or improve outcome of SCR.[70 71 73]

(13) Several retrospective studies suggest that *glucocorticoids* are associated with a higher risk of SRC. Blood pressure and renal function should be carefully monitored in patients with SSc treated with glucocorticoids (*strength of recommendation: C*).

Evidence regarding the impact of steroid use on the development of SRC comes mainly from retrospective studies, most of which showed significant association between steroid exposure and the occurrence of SRC.[67 70 71 74–77]

A case-control analysis including 220 patients with SSc showed that 36% of patients with SRC had received prednisone at a dose of 15 mg/day or more within 6 months preceding the onset of SRC, compared with 12% matched controls (OR; 95% CI 4.4; 2.1 to 9.4; p<0.001).[74]

Another analysis of the main risk factors for SRC suggested that patients with a high skin score, joint contractures and prednisone use (10 mg/day in 9 out of 10 patients) were at higher risk (43% vs 21% of patient without steroids) of SRC.[75]

In two more recent studies, including 518 and 410 patients with SSc, respectively, steroid use (adjusted OR; 95% CI 4.98; 1.52 to 16.3, p=0.008 and HR; 95% CI 1.105; 1.004 to 1.026, p=0.006, respectively) was an independent predictor of SRC.[71 76] A risk to develop SRC increased by 1.5% for every mg of prednisone/day consumed the trimester prior to SRC.[76]

A retrospective analysis including 140 patients with SRC showed that high doses of steroids (prednisone ≥30 mg/day) were used more frequently in patients with SSc with normotensive SRC (64%) as compared with those with hypertensive SCR (16%) suggesting an association between the use of high-dose steroids and the risk of normotensive SRC, which is associated with worse prognosis.[67]

The experts recognise that glucocorticoids, which are used in SSc, are part of the therapeutic strategy in the management of ILD, diffuse cutaneous disease or musculoskeletal involvement, although the evidence regarding their efficacy in SSc is limited.[78] Considering the potential risk of SRC associated with steroid use, *the experts recommend that patients with SSc treated with steroids should be carefully monitored with respect to the development of SRC.*

SSc-related GI disease

(14) Despite the lack of large, specific RCT, the experts recommend that *proton pump inhibitors* (PPIs) should be used for the treatment of SSc-related GI reflux and prevention of oesophageal ulcers and strictures (*strength of recommendation: B*).

Large, specific RCT for the efficacy of PPI in patients with SSc are lacking. A small RCT indicated that PPI may improve upper GI symptoms in patients with SSc.[79] The efficacy of PPI in the treatment of gastro-oesophageal reflux disease (GERD) in the general population is well documented in meta-analyses of RCTs.[80–82]

In asymptomatic patients with SSc, PPI should be used with caution since long-term therapy with PPIs might lead to nutritional deficiencies, possibly due to reduced intestinal absorption, or increased risk of infections.[83–85]

(15) Despite the lack of RCTs in patients with SSc, the experts recommend that *prokinetic drugs* should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction, etc) (*strength of recommendation: C*).

Small RCTs involving patients with SSc or CTD indicate that the short-term usage of cisapride has a beneficial effect on gastric emptying and lower oesophageal sphincter pressures.[86–90] However, in many countries cisapride has either been withdrawn or has limited access as a result of reports about long QT syndrome caused by cisapride, which predisposes to severe arrhythmias.[91]

Long-term efficacy RCTs of other prokinetics in SSc were not found. Several non-randomised or uncontrolled studies suggest that prokinetics may improve GI signs and symptoms in patients with SSc.[92–95]

Several prokinetic drugs have shown beneficial effects in RCTs involving patients with other than SSc-related dysmotility disorders or are under evaluation.[96 97]

The experts conclude that all available prokinetic drugs can be applied to patients with SSc with GI involvement on an individual basis, in consideration of potential benefit to risk ratio. Whether these drugs would be effective in the treatment of SSc-related symptomatic motility disturbances in a general manner is at present only speculative and needs urgently to be investigated.

(16) Despite the lack of RCTs in patients with SSc, the experts recommend the use of intermittent or rotating *antibiotics* to treat symptomatic small intestine bacterial overgrowth in patients with SSc (*strength of recommendation: D*).

Two small uncontrolled, non-randomised studies suggest that treatment with antibiotics might improve symptoms in patients with SSc with small intestine bacterial overgrowth (small intestinal bacterial overgrowth (SIBO)).[98 99] No RCTs regarding the efficacy of antibiotics in the treatment of SSc-related bacterial overgrowth or malabsorption were found.

In general, treatment of symptomatic small intestinal bacterial overgrowth is based on empirical courses of one or more broad-spectrum antibiotics with activity against both aerobic and anaerobic enterobacteria such as quinolones, amoxicillin-clavulanic acid, metronidazole, neomycin or doxycycline. The principles of diagnosis and treatment strategies of this condition have been summarised in an excellent review.[100]

Internal evaluation of recommendations

All task force members took part in the online-based evaluation of the updated recommendations. The results of this evaluation are presented in table 1. All but one recommendation received mean scores of more than 7 indicating high level of agreement. The mean score for the recommendation regarding fluoxetine for the treatment of SSc-related RP was 6.06, which is consistent with medium level of agreement.

Research agenda

In addition to the recommendations, the experts formulated a research agenda that addresses usage of pharmacological treatments in SSc or SSc-related organ complications, which were considered of particular interest (box 1). This research agenda can be helpful in developing further clinical research in SSc.

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DISCUSSION

As compared with the previous (2009) EULAR recommendations for treatment of SSc, the updated recommendations include several new treatments for specific SSc-related organ involvement. The greatest changes have been made in treatments of vascular complications of SSc and mirror the progress which had been made in this field during the last several years. These include the introduction of PDE-5 inhibitors for SSc-related RP and DUs, riociguat and new aspects for ERA, prostacyclin analogues and PDE-5 inhibitors for SSc-related PAH. The new recommendation regarding the use of fluoxetine for SSc-related RP was also added.

With regard to treatment of other than vascular complications of SSc, the recommendation for HSCT for selected patients with rapidly progressive SSc at risk of organ failure has been added.

Similar to the 2009 recommendations, the present recommendations address only pharmacological treatments which were considered most relevant and received consensus from the expert panel. As SSc is an uncommon and clinically heterogeneous disease, appropriate testing of therapies is difficult. Indeed, evidence supporting the present recommendations is often limited and some of the recommendations are supported by the evidence extrapolated from studies involving patients with diseases other than SSc or are based solely on expert opinion.

Similar to the 2009 recommendations, there are still not sufficient data to make specific recommendation for paediatric patients. It would be important to have studies at least for the effective paediatric dose of each medication, to be safely applied.

It should be recognised that there are several other promising therapies, including immunosuppressive drugs or new biological agents, which could not be included in the present recommendations because the evidence for their efficacy was considered insufficient at the time of developing these recommendations. The results of RCT evaluating new therapies in patients with SSc which were published after closure of the systematic literature research are presented in online supplementary table S4.

The first of these trials evaluated the efficacy of sildenafil in DUs healing in patients with SSc and is addressed in the comment following recommendation concerning treatment of DUs.[39]

Another double-blind, phase II RCT involved 87 patients with early diffuse SSc and elevated acute phase reactants. Treatment with tocilizumab (162 mg/week subcutaneously) was associated with a favourable trend in skin score improvement as compared with placebo after 24 weeks ($p=0.09$) and 48 weeks ($p=0.06$). In addition, encouraging changes in FVC were noted. In view of promising effects of tocilizumab on skin and lung involvement, it is concluded that further studies are warranted before definitive conclusions can be made about its risks and benefits in SSc.[101]

The results of another RCT, the SLS 2 comparing mycophenolate mofetil with CYC in patients with SSc-related ILD are expected to be published soon. The preliminary results of this study, recently published as an abstract of the 2015 ACR annual congress, indicate that mycophenolate mofetil (up to 3 g/day orally for 2 years) was comparable with oral CYC (2 mg/kg/day for 1 year followed by matching placebo for the second year) with regard to FVC course at 24th month.[102] However, final conclusions regarding the place of mycophenolate mofetil in the treatment of SSc-related ILD cannot yet be made. Other therapies, considered promising by the experts, were addressed in the research agenda (box 1). Since 'lack of evidence of efficacy' does not imply that 'efficacy is absent,' the absence of positive recommendation regarding specific drug should not be interpreted as a contraindication for its use.

It should also be emphasised that there are other treatment options, such as education, physiotherapy or local management of ischaemic lesions that were beyond the scope of the project or could not be included in the present recommendations due to lack of consensus among the experts.

In conclusion, it is believed that these updated recommendations will help to improve care of patients with SSc in an evidence-based way and indicate direction for further clinical research. Considering the significant complexity and heterogeneity of SSc and the limited evidence for treatments, it is recommended that patients with SSc should be referred to specialised centres with appropriate expertise in SSc management.

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Treatment Algorithms for Systemic Sclerosis According to Experts

Andreu Fernández-Codina,[1] Kyle M. Walker,[2] and Janet E. Pope,[3] on behalf of the Scleroderma Algorithm Group

Objective. **There is a lack of agreement regarding treatment for many aspects of systemic sclerosis (SSc). We undertook this study to generate SSc treatment algorithms endorsed by a high percentage of SSc experts.**

Methods. **Experts from the Scleroderma Clinical Trials Consortium and the Canadian Scleroderma Research group (n = 170) were asked whether they agreed with SSc algorithms from 2012. Two consensus rounds refined agreement; 62, 54, and 48 experts (36%, 32%, and 28%, respectively) completed the first, second, and third surveys, respectively.**

Results. **For treatment of scleroderma renal crisis, 81% of experts agreed (first-, second-, and third-line treatments were angiotensin-converting enzyme inhibitors, then adding calcium-channel blockers [CCBs], then adding angiotensin receptor blockers [ARBs], respectively). For pulmonary arterial hypertension (PAH), 81% of experts agreed (for mild PAH, treatments were phosphodiesterase 5 [PDE5] inhibitors, then endothelin receptor antagonists plus PDE5 inhibitors, then prostanoids, respectively; for severe PAH, prostanoids were first-line treatment). For mild Raynaud's phenomenon (RP), 79% of experts agreed (treatments were CCBs, then adding PDE5 inhibitors, then ARBs or switching to another CCB, respectively; after the third line of treatment, mild RP was deemed severe). For severe RP, the first- through fourth-line treatments were CCBs, then adding PDE5 inhibitors or prostanoids, then adding PDE5 inhibitors (if not added as second-line treatment) or prostanoids (if not added as second-line treatment), then switching to another CCB, respectively. For active treatment of digital ulcers, 66% of experts agreed (first- and second-line treatments were CCBs and PDE5 inhibitors, respectively). For interstitial lung disease, 69% of experts agreed (for induction therapy, treatments were mycophenolate mofetil [MMF], intravenous cyclophosphamide [IV CYC], and rituximab, respectively; for maintenance, first-line treatment was MMF). For skin involvement, 71% of experts agreed (for a modified Rodnan skin thickness score [MRSS] of 24, first- and second-line treatments were methotrexate [MTX] and MMF, respectively; for an MRSS of 32, first- through fourth-line treatments were MMF, MTX, IV CYC, and hematopoietic stem cell transplantation, respectively). For inflammatory arthritis, 79% of experts agreed (first- through fourth-line treatments were MTX, low-dose glucocorticoids, hydroxychloroquine, and rituximab or tocilizumab, respectively). Algorithms for cardiac and gastrointestinal involvement had ≥75% agreement.**

Conclusion. **Total agreement for SSc algorithms was considerable. These algorithms may guide treatment.**

Systemic sclerosis (SSc; scleroderma) is an autoimmune connective tissue disease characterized by autoantibodies, fibrosis, and microvascular injury and endothelial cell activation that result in vascular damage. Vascular injury induces both innate and acquired immune responses, resulting in fibroblast activation and organ fibrosis (1). SSc may target multiple organs, including the skin, lungs, heart, vascularization, kidneys, gastrointestinal tract, and musculoskeletal structures (2). Mortality among scleroderma patients is significant, with a standardized mortality ratio (SMR) of 3.5 in studies of prevalent cases (3). This mortality may be

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increased in the early years of the disease, reaching an SMR of 4 in a multinational inception cohort (4). In general, treatment strategies target involved organs as early as possible to avoid damage. Many treatment options are available for each manifestation, but evidence with respect to the order of treatment is scarce. Current management guidelines have some gaps regarding second-line treatment, combinations, and proposed algorithms (5).

In 2012, several algorithms for SSc treatment were developed by a consensus of international experts (6). The goal was to provide a consensus for treatment options in SSc management in usual practice. Since new therapeutic advances have been developed, we intended to review and update the previous expert-assessed algorithms.

METHODS

The surveys were conducted between August 2016 and September 2017. A complete list of SSc experts participating in the Scleroderma Clinical Trials Consortium (SCTC) and/or in the Canadian Scleroderma Research Group (CSRG) was obtained. All the participants received the first survey in 2 separate e-mails (Figure 1). All those who answered the previous survey were invited to complete the next one, and so on. The collaborators who completed the 3 surveys were listed as authors in the Scleroderma Algorithm Group. A list of Scleroderma Algorithm Group authors is provided in Appendix A.

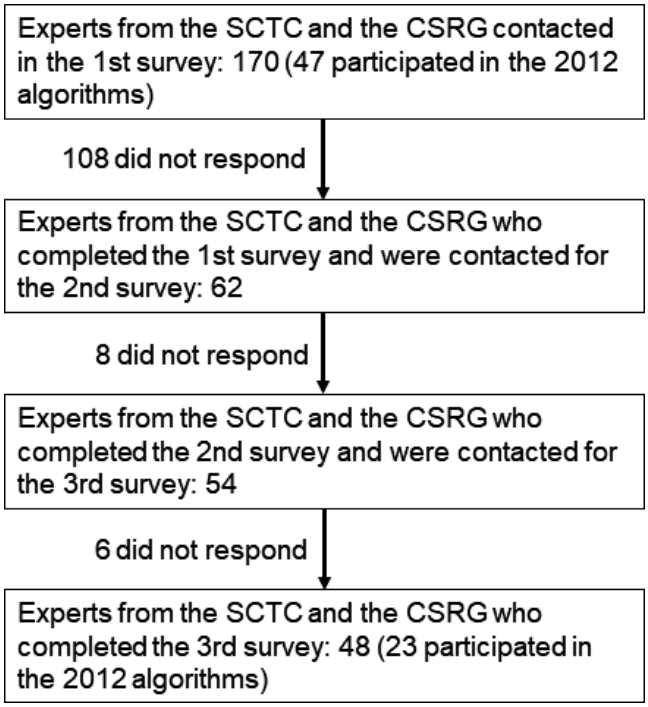
Experts from the SCTC and the CSRG contacted in the 1st survey: 170 (47 participated in the 2012 algorithms)
108 did not respond
Experts from the SCTC and the CSRG who completed the 1st survey and were contacted for the 2nd survey: 62
8 did not respond
Experts from the SCTC and the CSRG who completed the 2nd survey and were contacted for the 3rd survey: 54
6 did not respond
Experts from the SCTC and the CSRG who completed the 3rd survey: 48 (23 participated in the 2012 algorithms)

Figure 1. Flow chart of the systemic sclerosis algorithm surveys. For the 2012 algorithms, see ref. 6. SCTC = Scleroderma Clinical Trials Consortium; CSRG = Canadian Scleroderma Research Group.

We designed 3 consecutive surveys using Google forms. The first survey was based on the previous 2012 algorithms (6). Experts were questioned on demographics (age, sex, specialty, years of practice, practice setting, management of SSc patients, number of SSc patients in their practice, number of SSc referrals per year) and if they agreed (yes/no/minor modifications) with each of the 2012 organ-based SSc treatment algorithms. In case they did not agree, spaces for free text were provided for each line of treatment to provide their treatment preferences. The SSc algorithms included scleroderma renal crisis (SRC), pulmonary arterial hypertension (PAH), Raynaud's phenomenon (RP), interstitial lung disease (ILD), gastrointestinal (GI) involvement, skin involvement, and inflammatory arthritis. No previous algorithm was available for cardiac involvement; therefore, each respondent stated what he or she would use as first-line, second-line, and further treatment for various cardiac scenarios (such as treatment for pericardial involvement, myocardial dysfunction, and conduction alterations).

The second survey provided the frequencies with which respondents from the first survey agreed, along with suggested modifications (represented in a modified algorithm if the number of experts who disagreed was higher than the number of those who agreed; otherwise, the suggested changes were reflected in a notation to the previous algorithm). Experts were asked if they would add the next treatment or just switch to the next treatment for second- to fifth-line treatments depending on each algorithm. A semiquantitative approach was used to ask questions regarding dosing for prednisone and nifedipine (chosen as the most representative drugs of their respective classes). The GI involvement algorithm was completely redesigned after suggestions from the participants to cover distinct manifestations. This new algorithm was included in the second survey. Experts were asked to rate their agreement, and some extra open questions were added regarding likely modifications and use of prokinetics.

A third survey was conducted to show the likely final configuration of the algorithms, open to minor modifications. Minor modifications were made to pool different treatment options with similar agreement rates in the same line of treatment to increase the agreement rate among participants. Unfortunately, due to database design issues (missing identification in the first survey), we were unable to link the demographic information collected at the first survey with some experts who completed the 3 surveys.

There were no definitions for each organ involved. Algorithms were provided by experts asking which treatment they would use first, then which second treatment, and so on, under the assumption that there was no contraindication to treatment. Grading agreement was not predetermined.

RESULTS

Percentages of experts responding to surveys. One hundred seventy SSc experts received the survey. Sixty-two, 54, and 48 experts completed the first, second, and third surveys, respectively. Thirty-six percent of the experts responded to the first survey, 87% of those who responded to the first survey responded to the second survey, and 89% of those who responded to the second survey responded to the third survey. The demographic

and practice characteristics of the respondents are summarized in Table 1. The final percentages of agreement for the 2012 and 2017 algorithms are shown in Table 2.

SRC. The initial agreement after the first survey was 69%. The algorithm was simplified, but no major changes were made (Figure 2A). Eighty-one percent of the experts agreed with this algorithm after the third survey. It is important to mention that before every new add-on to the treatment, the previous antihypertensive medication should have been well tolerated and should have had some benefit. The blood pressure (BP) goals were 140/85 mm Hg for 39% of respondents or ≤120/80 mm Hg for 37% of respondents; only 9.3% of respondents would target a higher BP (150/90 mm Hg). The time to obtain the target BP was <24 hours for 15% of respondents, 24–48 hours for 44%, 48 hours to 1 week for 33%, and >1 week for 7%. Approximately half of respondents (36 of 62) would not prescribe angiotensin-converting enzyme (ACE) inhibitors during pregnancy.

Table 1. Characteristics of the respondents comparing the first and final rounds*

	First survey (n = 62)	Third survey (n = 32)†
Practice		
Community based	2 (3)	1 (3)
University based	59 (95)	30 (94)
Other	1 (2)	1 (3)
Sex		
Female	32 (52)	14 (45)
Male	30 (48)	17 (55)
Specialty		
Rheumatology	55 (90)	26 (84)
Pediatric rheumatology	1 (2)	1 (3)
Internal medicine	4 (7)	3 (10)
Other	1 (2)	1 (3)
Years in practice		
<5	2 (3)	0 (0)
5–10	7 (11)	5 (16)
11–15	12 (20)	6 (19)
16–20	3 (5)	2 (7)
>20	37 (61)	18 (59)
SSc patients per year		
<30	2 (3)	2 (7)
31–50	5 (8)	2 (7)
51–100	18 (29)	7 (23)
101–200	10 (16)	6 (19)
201–300	12 (19)	7 (23)
301–400	9 (14)	3 (10)
>400	6 (10)	4 (13)
New SSc patients per year		
<10	8 (13)	4 (13)
11–25	22 (35)	12 (39)
26–50	19 (31)	9 (29)
51–100	9 (14)	3 (10)
>100	4 (6)	3 (10)

* Values are the number (%). SSc = systemic sclerosis.
† Forty-eight experts responded to the third survey, but data for 16 of them were not identifiable due to database design problems.

Table 2. Comparison of agreement on treatment guidelines from the previous report with agreement obtained in the current study*

Algorithms for SSc treatment	Agreement in 2012, %†	Agreement in 2017, %
Scleroderma renal crisis	69	81
Pulmonary arterial hypertension	45	81
Raynaud's phenomenon	66	79
Digital ulcers	58	66
Interstitial lung disease	64	69
Gastrointestinal involvement	NA	77
Skin involvement	56, 40, 36‡	71
Inflammatory arthritis	45	79
Cardiac involvement	NA	75

* Agreement is the percentage of experts who agreed to the algorithm. SSc = systemic sclerosis; NA = not applicable.
† See ref. 6.
‡ For modified Rodnan skin thickness scores of 10, 24, and 32, respectively.

ACE inhibitors are used for first-line SRC treatment. Experts proposed adding calcium-channel blockers (CCBs) only after first-line treatment to gain rapid control of hypertension. Regarding CCBs, initial doses of nifedipine at 30 mg extended release once daily (37% of respondents) or 10 mg 3 times daily (30% of respondents) were the preferred options. Doses of 30 mg extended release twice daily and 20 mg 3 times daily accounted for 11% and 22%, respectively, of the experts.

PAH. The original algorithm for mild PAH had a 45% acceptance rate in the first survey, while that for severe PAH had 64% agreement. In mild PAH, phosphodiesterase 5 (PDE5) inhibitors replaced endothelin receptor antagonists (ERAs) as the first-line treatment (Figure 3B). As an alternative, the initial combination of ERAs and PDE5 inhibitors was proposed by 23% of the experts. ERAs were second-line treatment and prostanoids stayed as third-line treatment. Provided that the previous treatment was well tolerated, adding treatment was the most common practice if the PAH target was not achieved. In severe PAH, 27% of the experts would advocate for the combination of ERAs and PDE5 inhibitors as first-line treatment. Lung transplantation with or without heart transplantation was incorporated as a fourth line of treatment. Overall, after the third survey, the final agreement rate was 81%. The use of oral anticoagulants in SSc patients for PAH was infrequent (6% of experts for always, 28% for occasionally, 30% for rarely, and 37% for never). If anticoagulation was used for PAH, 60% would use warfarin, 7% would use direct action anticoagulants, and 31% would use either class of anticoagulant.

RP. Fifty-two percent of the experts agreed with the old algorithm for mild RP, and 66% agreed with the severe RP algorithm. After the third line of treatment,

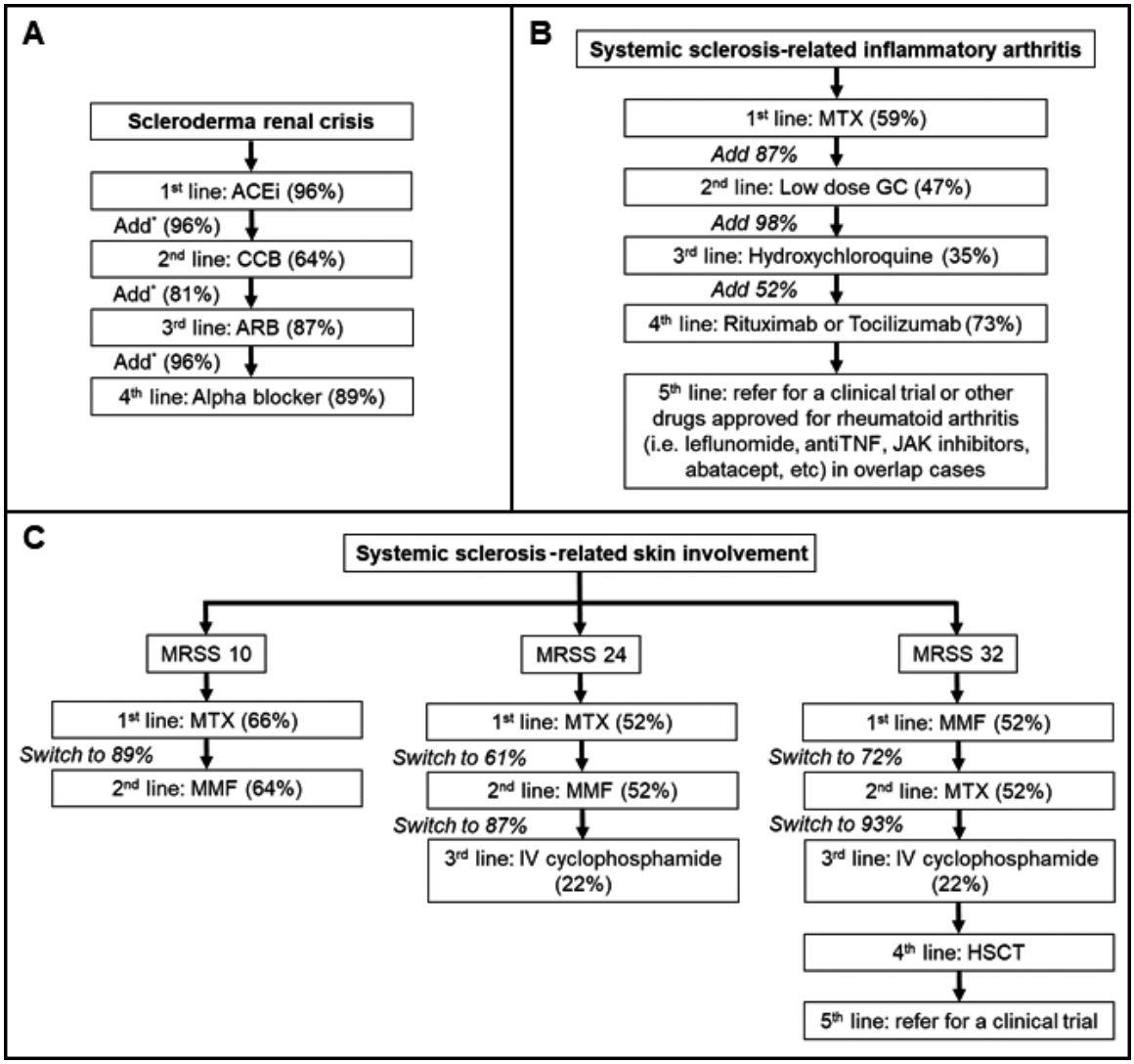

Figure 2. Algorithms for the treatment of systemic sclerosis (SSc) renal crisis (**A**), SSc-related inflammatory arthritis (**B**), and SSc-related skin involvement (**C**). ACEi = angiotensin-converting enzyme inhibitor; CCB = calcium-channel blocker; ARB = angiotensin receptor blocker; MTX = methotrexate; GC = glucocorticoid; anti-TNF = anti–tumor necrosis factor; MRSS = modified Rodnan skin thickness score; MMF = mycophenolate mofetil; IV = intravenous; HSCT = hematopoietic stem cell transplantation. * = only if the previous drug was tolerated and gave some benefit.

mild RP was deemed severe (Figure 3C). Digital sympathectomy and botulinum toxin infiltrations were included as a fifth line of treatment, although this was more controversial. Only 44% of the experts occasionally recommended digital sympathectomy. Recommendations for other potential RP treatment varied (58% of experts), including aspirin (75% of experts), statin (29%), fluoxetine (21%), and pentoxifylline (7%). Respondents were asked about use of topical nitrates; 54% said they would consider their use, mostly as topical paste (62%) applied in the interdigital areas. The modified algorithm resulted in 79% agreement.

Digital ulcers. Agreement with the 2012 algorithm was 58% for digital ulcer prevention and 40% for active treatment of digital ulcers. The prevention algorithm was simplified without major changes (Figure 3D). The active treatment scheme incorporated prostanoids as third-line treatment. The final overall expert agreement increased to 66%, although 34% suggested minor modifications.

ILD. Only 24% of the participants agreed with the previous ILD induction therapy algorithm, while 64% agreed with the maintenance proposal. Mycophenolate mofetil (MMF) replaced intravenous cyclophosphamide (IV CYC) as first-line induction therapy (Figure 3A).

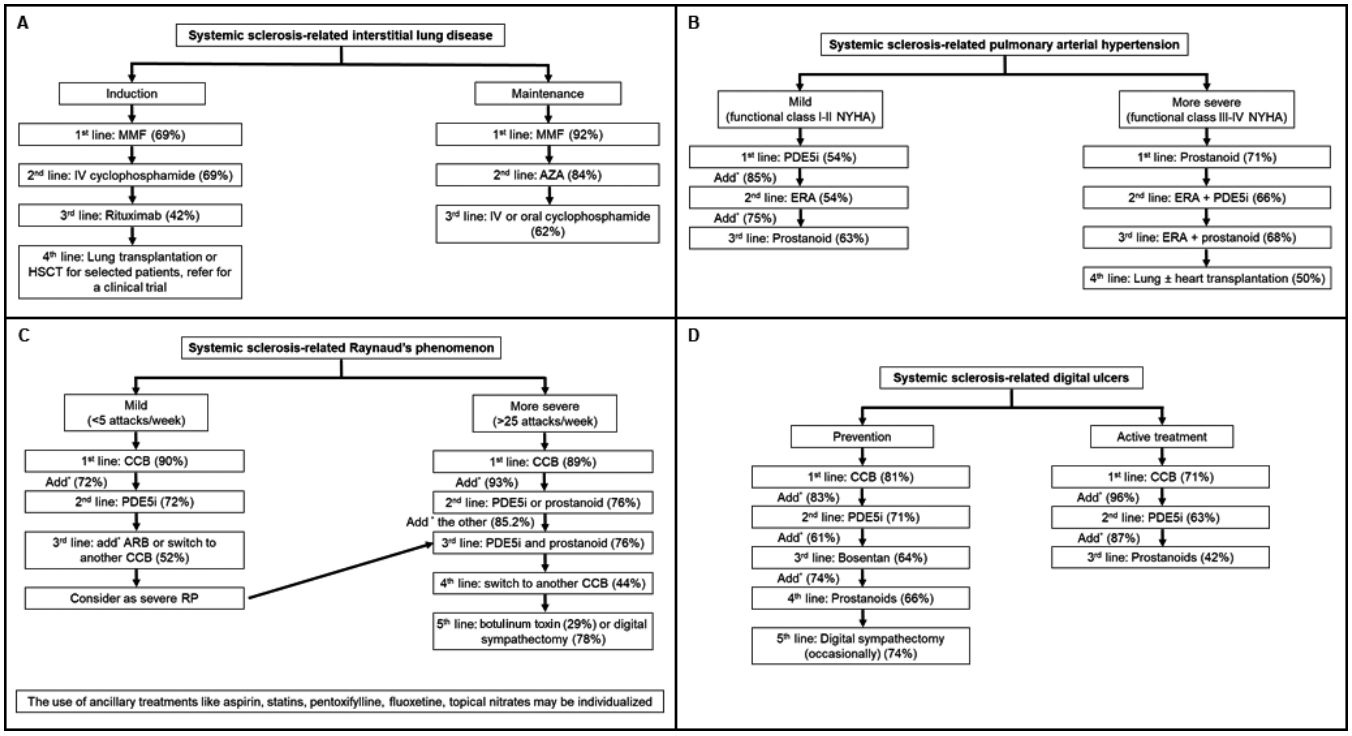
A
Systemic sclerosis-related interstitial lung disease
Induction
1st line: MMF (69%)
2nd line: IV cyclophosphamide (69%)
3rd line: Rituximab (42%)
4th line: Lung transplantation or HSCT for selected patients, refer for a clinical trial
Maintenance
1st line: MMF (92%)
2nd line: AZA (84%)
3rd line: IV or oral cyclophosphamide (62%)
B
Systemic sclerosis-related pulmonary arterial hypertension
Mild (functional class I-II NYHA)
1st line: PDE5i (54%)
Add* (85%)
2nd line: ERA (54%)
Add* (75%)
3rd line: Prostanoid (63%)
More severe (functional class III-IV NYHA)
1st line: Prostanoid (71%)
2nd line: ERA + PDE5i (66%)
3rd line: ERA + prostanoid (68%)
4th line: Lung ± heart transplantation (50%)
C
Systemic sclerosis-related Raynaud's phenomenon
Mild (<5 attacks/week)
1st line: CCB (90%)
Add* (72%)
2nd line: PDE5i (72%)
3rd line: add* ARB or switch to another CCB (52%)
Consider as severe RP
More severe (>25 attacks/week)
1st line: CCB (89%)
Add* (93%)
2nd line: PDE5i or prostanoid (76%)
Add* the other (85.2%)
3rd line: PDE5i and prostanoid (76%)
4th line: switch to another CCB (44%)
5th line: botulinum toxin (29%) or digital sympathectomy (78%)
The use of ancillary treatments like aspirin, statins, pentoxifylline, fluoxetine, topical nitrates may be individualized
D
Systemic sclerosis-related digital ulcers
Prevention
1st line: CCB (81%)
Add* (83%)
2nd line: PDE5i (71%)
Add* (61%)
3rd line: Bosentan (64%)
Add* (74%)
4th line: Prostanoids (66%)
5th line: Digital sympathectomy (occasionally) (74%)
Active treatment
1st line: CCB (71%)
Add* (96%)
2nd line: PDE5i (63%)
Add* (87%)
3rd line: Prostanoids (42%)

Figure 3. Algorithms for the treatment of systemic sclerosis–related interstitial lung disease (**A**), pulmonary arterial hypertension (**B**), Raynaud's phenomenon (RP) (**C**), and digital ulcers (**D**). Note that in some countries or regions, certain drugs (i.e., prostanoids or bosentan) may have prescription restrictions or may not be available. MMF = mycophenolate mofetil; IV = intravenous; HSCT = hematopoietic stem cell transplantation; AZA = azathioprine; NYHA = New York Heart Association; PDE5i = phosphodiesterase 5 inhibitor; ERA = endothelin receptor antagonist; CCB = calcium-channel blocker; ARB = angiotensin receptor blocker. * = only if blood pressure is not low and previous drug was tolerated and gave some benefit.

Rituximab was added as the third option, and the possibility of hematopoietic stem cell transplantation (HSCT) in selected cases or for clinical trial referral was open for nonresponding patients. Maintenance treatment for ILD did not show significant changes in agreement. In the final survey, 69% of the experts agreed with the modified algorithm.

Use of glucocorticoids (GCs) in ILD induction therapy was not common (11% of experts would use them always, 28% sometimes, 24% occasionally, and 37% never). Among the experts who would use GCs in ILD induction therapy, 41% would treat with prednisone at <7.5 mg/day, 46% at 7.5–20 mg/day, and 13% at >20 mg/day. GC treatment would be prescribed for <3 months by 42%, for 3–6 months by 33%, and for >6 months by 8%.

GI involvement. The original algorithm was redesigned to cover more GI manifestations. The new algorithm had 77% agreement (Figure 4A). Agreement among experts varied for first-line promotility agents (metoclopramide 44%, domperidone 31%, erythromycin 15%, octreotide 15%) and for antibiotics (metronidazole 60%, ciprofloxacin 60%, rifaximin 35%, doxycycline 23%).

Skin involvement. Agreement rates with the 2012 algorithms for SSc skin involvement in 3 different patient scenarios were 56% for patients with a modified Rodnan skin thickness score (MRSS) (7) of 10, 40% for those with an MRSS of 24, and 35% for those with an MRSS of 32. The skin score scenarios were to mimic mild, moderate, and severe skin disease activity. The final results for first-line treatments were close (Figure 2C), especially for an MRSS of 24 (agreement of 52% for methotrexate [MTX] and 48% for MMF) and an MRSS of 32 (agreement of 52% for MMF and 48% for MTX). Most of the experts would switch from one treatment to the next. For an MRSS of 32, IV CYC was considered third-line treatment and HSCT was considered fourth-line treatment, while nonresponding patients or those eligible for HSCT would be candidates for a clinical trial. Agreement reached 71%.

Experts were questioned about the concomitant use of GCs for skin treatment. Thirteen percent prescribed them always, 19% sometimes, 33% occasionally, and 35% never. Among the experts who would use GCs, 49% would suggest prednisone at <7.5 mg/day, and 51% would suggest prednisone at 7.5–20 mg/day.

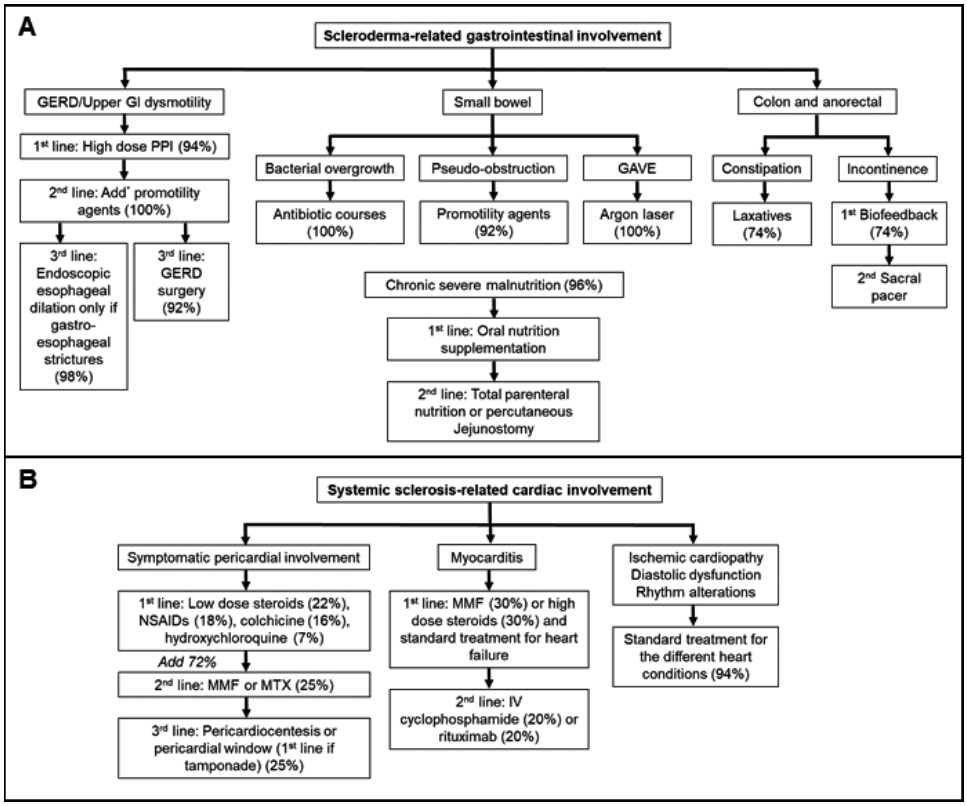
A
Scleroderma-related gastrointestinal involvement
GERD/Upper GI dysmotility
1st line: High dose PPI (94%)
2nd line: Add* promotility agents (100%)
3rd line: Endoscopic esophageal dilation only if gastro-esophageal strictures (98%)
3rd line: GERD surgery (92%)
Small bowel
Bacterial overgrowth
Antibiotic courses (100%)
Pseudo-obstruction
Promotility agents (92%)
GAVE
Argon laser (100%)
Chronic severe malnutrition (96%)
1st line: Oral nutrition supplementation
2nd line: Total parenteral nutrition or percutaneous Jejunostomy
Colon and anorectal
Constipation
Laxatives (74%)
Incontinence
1st Biofeedback (74%)
2nd Sacral pacer
B
Systemic sclerosis-related cardiac involvement
Symptomatic pericardial involvement
1st line: Low dose steroids (22%), NSAIDs (18%), colchicine (16%), hydroxychloroquine (7%)
Add 72%
2nd line: MMF or MTX (25%)
3rd line: Pericardiocentesis or pericardial window (1st line if tamponade) (25%)
Myocarditis
1st line: MMF (30%) or high dose steroids (30%) and standard treatment for heart failure
2nd line: IV cyclophosphamide (20%) or rituximab (20%)
Ischemic cardiopathy
Diastolic dysfunction
Rhythm alterations
Standard treatment for the different heart conditions (94%)

Figure 4. Algorithms for the treatment of systemic sclerosis (SSc)–related gastrointestinal (GI) involvement (**A**) and SSc-related cardiac involvement (**B**). GERD = gastroesophageal reflux disease; PPI = proton-pump inhibitor; GAVE = gastric antral vascular ectasia; NSAIDs = nonsteroidal antiinflammatory drugs; MMF = mycophenolate mofetil; MTX = methotrexate; IV = intravenous. * = only if the previous drug was tolerated and gave some benefit.

Inflammatory arthritis. Forty-five percent of the experts agreed with the initial algorithm for inflammatory arthritis. Multiple first-line treatment options were used by the participants, but MTX was the most commonly used (59%), followed by hydroxychloroquine (27%). GCs might be prescribed by 75% of the experts and nonsteroidal antiinflammatory drugs by 77%, if these were not contraindicated or if there were no safety concerns. GCs in low doses (54% would treat with prednisone at <7.5 mg/day and 41% at 7.5–20 mg/day) for a short period (67% would prescribe for <3 months, 8% for 3–6 months, and 25% for >6 months) were part of second-line treatment for inflammatory arthritis. Biologic agents (rituximab and tocilizumab) were introduced into the algorithm for fourth-line treatments, and other advanced treatments for patients with features of rheumatoid arthritis (RA) were left as fifth-line treatments. Most participants (79%) agreed with the algorithm (Figure 2B).

Cardiac involvement. No previous algorithm was available. The main conditions included were symptomatic pericardial involvement, myocarditis, ischemic cardiopathy, diastolic dysfunction, and rhythm/conduction alterations (Figure 4B). Specific expert recommendations were made for symptomatic pericardial involvement and myocarditis. The final agreement was 75%.

DISCUSSION

The low prevalence of SSc (8) and the limited treatment algorithms available, especially after first-line treatments have failed, may lead to variations in SSc management. The main causes of death among SSc patients are PAH, ILD, cardiac involvement, and cancer (8). Most of the treatments available are organ-based therapies that were originally indicated for other conditions, but multiple new drugs are currently in the pipeline (9). Treatment may modify the natural history of SSc (10). The heterogeneous features of SSc may make trials challenging (11). The current guidelines for treatment of SSc are those of the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) (12) and the updated European League Against Rheumatism (EULAR) recommendations (13), published in 2016 and 2017, respectively. The treatment algorithms are not

meant to contradict SSc or other organ-specific guidelines. The suggestions by experts for therapy reported herein intend to provide consensus in SSc where there is uncertainty regarding therapy and to provide information about current practice using the drugs available. Many clinical trials do not provide treatment after first- or second-line standard therapy has failed.

In the present study, we updated the 2012 algorithms according to experience of experts in SSc. Algorithms include those for SRC, PAH, RP, ILD, GI involvement, skin involvement, inflammatory arthritis, and cardiac involvement. In general, the agreement has remained the same for many organ treatment algorithms, but some, such as that for treatment of PAH, have improved. Some new trends and advances in SSc treatment are reflected in the evolution of the algorithms. These recommendations may help clinicians in dealing with situations in which evidence supporting one treatment versus another is weak and guidelines fall short.

The rate of response to the first survey was modest. Most of the 62 experts who responded to the first survey responded to the subsequent surveys. Given the similarity of the expert panel composition between the first and third surveys, dropouts did not seem to diminish the global expertise. We did not define agreement rates a priori, but we thought that they were mostly fair to good (69–82%).

Differences in practice have been described between SSc experts and general rheumatologists who occasionally see SSc patients (14). Even among experienced centers, practices vary by center size (15). Experienced clinicians who contributed to the algorithms were mainly at university centers, where only 15% see fewer than 50 SSc patients annually. The characteristics of the respondents are comparable to those of the respondents who participated in the 2012 study (6).

SRC algorithms did not change substantially over time. The present algorithm is simpler because the drugs used for both severe and mild SRC were the same and agreement improved from 66% to 81%. No major changes to SRC treatment have been reported since the introduction of ACE inhibitors (16). Rapid control of BP should be a target with the addition of other antihypertensive agents to ACE inhibitors. In the present survey, CCBs replaced angiotensin receptor blockers as the second line of treatment (to be added to the first line). Although ACE inhibitors may increase the risk of fetal malformations in pregnancy, 40% of the experts would keep using them if a patient had previous SRC due to the chance of recurrence with discontinuation of ACE inhibitors. Consensus might be improved if there was universal access to drugs and if the experts had a face-to-face meeting to further discuss points of view where differences exist.

PAH treatment algorithms have evolved since the 2012 study. Previously, after monotherapy failed, a combination of drugs was accepted for severe PAH (9). In 2017, the AMBITION study, a phase III/IV double-blind randomized clinical trial that evaluated the use of combined ambrisentan and tadalafil as an initial treatment for class II/III PAH (including SSc patients), demonstrated more improvement in the combination arm (17). This combination (or other combinations of ERAs and PDE5 inhibitors) could potentially replace prostanoids as the first option in severe PAH. Riociguat, a guanylate cyclase stimulator, has been approved to treat PAH and connective tissue disease–related PAH (18). Only a minority of experts recommended riociguat (possibly due to incomplete access to the drug and less experience with it), but its use may increase in the future. Finally, lung transplantation (occasionally along with heart transplantation), which appears to be a valid treatment option for selected patients with end-stage PAH or ILD (19), was included as a fourth-line treatment for severe ILD.

Treatment for RP has remained without major changes. Ancillary treatments for RP may be introduced along with the treatments in the algorithms. An important consideration is that side effects are fewer and financial costs are lower in comparison with more advanced treatments like PDE5 inhibitors or prostanoids.

Prevention of digital ulcers was simplified in comparison with the previous algorithm. Macitentan was not effective in preventing digital ulcers (20), so only bosentan was included in the algorithm. Regarding active treatment of digital ulcers, prostanoids were third-line treatment, although a meta-analysis only showed a trend toward significance in digital ulcer healing with IV iloprost (21). Use of prostanoids to treat digital ulcers also appears in SSc guidelines (12,13).

Management of ILD induction therapy has changed considerably. After the Scleroderma Lung Studies (SLS 1 and SLS 2) (22), experts have changed their first-line preference from CYC to MMF. Oral CYC was used in the SLS studies, but the majority of experts said that if they used CYC, it would be mostly IV. There are more adverse events with oral CYC than with IV CYC. Some experts suggested the use of oral CYC either if IV CYC was not feasible or due to the severity of the disease. The use of rituximab as a rescue therapy is also increasing, with some observational data supporting its effectiveness in this context (23). Tocilizumab was only occasionally suggested, and this could be due to results of a phase III trial not yet being available along with a lack of experience and access currently in routine practice (24). The fourth line of treatment may include referral for ongoing clinical trials and HSCT for selected patients (25). Experts may have less experience

with this last option due to high treatment-related morbidity, requirement of specialized teams, and uncertain benefits for ILD. Some experts (60%) may prescribe GCs to patients with ILD (possibly those with fast-progressing lung fibrosis), using moderate-to-low doses often for <6 months.

Multiple treatments for GI involvement were used by experts in their daily practice for dysmotility/gastroesophageal reflux disease and bacterial overgrowth. Randomized clinical trial data are lacking for the best treatment approach in SSc for various GI complications.

The use of GCs among experts was not high in our study; however, they have been used more frequently in some trials (22). Experts incorporated MMF (as first-line treatment) and IV CYC (as third-line treatment) to treat SSc patients with high MRSS scores. There is weak evidence favoring the use of immunosuppression in early diffuse cutaneous SSc (dcSSc) (26). Experts have incorporated the possibility of performing HSCT (25). In skin involvement, randomized clinical trials show a clear benefit of HSCT versus IV CYC, but it is only a later line of treatment due to its risks (27). Recruitment for clinical trials may be an option given the lack of consistently effective treatment in early dcSSc.

Treatment for inflammatory arthritis was similar to treatment for RA, such as disease-modifying antirheumatic drugs, low-dose GCs, and biologic agents, as suggested in the BSR and BHPR guideline (12). Advanced treatments like tocilizumab, abatacept, and rituximab might have a role for refractory arthritis or patients with overlapping RA (28).

There is no randomized clinical trial evidence for treatment of cardiac involvement in SSc. Many cardiac manifestations, such as congestive heart failure, are treated similarly to other causes of heart failure. Pericarditis and myocarditis in SSc seemed to be treated by experts as inflammatory complications. Small pericardial effusions often accompany other serious organ involvement such as SRC or PAH, and in these cases they are usually not inflammatory and not treated, but they may be a poor prognostic marker (due to the other organs involved).

Expert practices may differ in the treatment options available according to geographic and socioeconomic restrictions. There was a predominance of North American (n = 27) and European (n = 17) experts, reflecting the composition of the SCTC and CSRG. The initial response rate was 36% in those surveyed, but it may be that 62 SSc experts provide enough variation in opinions with respect to treatment. However, we don't know if results would differ if the response rate was higher. After the first questionnaire, those who responded were invited to participate further in the study and their retention was good. Moreover, experts in respirology, cardiology, gastroenterology, nephrology, or other specialties were not consulted. The treatments reported are what are currently being prescribed for SSc patients, and they may or may not reflect what is being prescribed by other specialists. A limitation is that some treatment is based on expert opinion. For instance, the use of CCBs as first-line treatment for digital ulcers differs from the EULAR recommendations (13). Delphi exercises can get close to consensus, but total agreement is not likely.

A strength of our study is that there was a large sample of experts reflecting a broad range of opinions, and agreement was still frequently high. These algorithms may be superseded by specific situations such as drug intolerance, treatment failure, drug access, and clinical judgment, so they can serve as a guide to treatment in SSc. The latest PAH guidelines make some recommendations that are not immediately available for most of the regional health care systems due to financial and approval issues. It is possible that treatment recommendations for PAH (such as ambrisentan, selexipag, and riociguat) have not yet been incorporated for all patients.

In conclusion, we have updated our previous algorithms for treatment of SSc, reaching a higher level of overall agreement and providing therapeutic options for real-world situations, especially where high-quality evidence is not available.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Pope had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Fernández-Codina, Walker, Pope.
Acquisition of data. Fernández-Codina, Walker, Pope.
Analysis and interpretation of data. Fernández-Codina, Walker, Pope.

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OPEN ACCESS

Consensus-based recommendations for the management of juvenile localised scleroderma

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ABSTRACT

In 2012, a European initiative called Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) was launched to optimise and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. Juvenile localised scleroderma (JLS) is a rare disease within the group of paediatric rheumatic diseases (PRD) and can lead to significant morbidity. Evidence-based guidelines are sparse and management is mostly based on physicians' experience. This study aims to provide recommendations for assessment and treatment of JLS. Recommendations were developed by an evidence-informed consensus process using the European League Against Rheumatism standard operating procedures. A committee was formed, mainly from Europe, and consisted of 15 experienced paediatric rheumatologists and two young fellows. Recommendations derived from a validated systematic literature review were evaluated by an online survey and subsequently discussed at two consensus meetings using a nominal group technique. Recommendations were accepted if ≥80% agreement was reached. In total, 1 overarching principle, 10 recommendations on assessment and 6 recommendations on therapy were accepted with ≥80% agreement among experts. Topics covered include assessment of skin and extracutaneous involvement and suggested treatment pathways. The SHARE initiative aims to identify best practices for treatment of patients suffering from PRDs. Within this remit, recommendations for the assessment and treatment of JLS have been formulated by an evidence-informed consensus process to produce a standard of care for patients with JLS throughout Europe.

INTRODUCTION

In 2012, a European project called Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) was launched to optimise and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases.[1] As currently no international or European consensus exists with regard to the assessment and treatment of juvenile rheumatic diseases, defining clear guidelines is one of the most important aims of the SHARE initiative. In this paper, we focus on juvenile localised scleroderma (JLS) consensus-based recommendations.

METHODS

An international committee of 15 experts in paediatric rheumatology was established to develop consensus-based recommendations for JLS.[2] European League Against Rheumatism (EULAR) standard operating procedures for developing best practice were used.[3] Ten experts were part of the SHARE consortium; five other experts were asked to take part to the project due to their consolidate clinical experience in the management of JLS.

Systematic literature search

The electronic databases PubMed/MEDLINE, Embase and Cochrane were searched in August 2013 and subsequently in January 2015. All synonyms of JLS were searched in MeSH/Emtree terms, title and abstract. Reference tracking was performed in all included studies (full search strategy in online supplementary figure S1). Fellows (RC, FS) and experts (FZ, IF) selected the relevant papers for validity assessment (inclusion and exclusion criteria shown in online supplementary figure S1): 53 out of 1550 papers were eventually selected. All full-text scored papers are listed in the online supplementary list 1.

Validity assessment

Every relevant paper dealing with 'diagnosis', 'assessment' and 'therapy' studies has been independently assessed for methodological quality by two experts, who extracted data using a predefined scoring system.[4] Disagreements were resolved by the opinion of a third expert. Adapted classification tables for assessment and therapeutic studies were used to determine the level of evidence and strength of each recommendation.[5]

Recommendation development

As part of the EULAR standard operating procedure,[3] experts assessed validity and level of evidence and described the main results and conclusions of each paper. This information was examined by two experts (FZ, IF) and used to formulate 18 provisional recommendations. These drafted recommendations were at first presented to the expert committee in an online survey (100% response rate) and subsequently revised accordingly to responses. The derived recommendations were then presented to the expert committee and discussed using a nominal group technique in two face-to-face

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Table 1 Recommendations regarding diagnosis and assessment

		L	S	Agreement (%)
	Overarching principle			
	All children with suspected localised scleroderma should be referred to a specialised paediatric rheumatology centre.	4	D	100
1	LoSSI, which is part of LoSCAT, is a good clinical instrument to assess activity and severity in JLS lesions and is highly recommended in clinical practice.	3	C	90
2	LoSDI, which is part of LoSCAT, is a good clinical instrument to assess damage in JLS and is highly recommended in clinical practice.	3	C	90
3	Infrared thermography can be used to assess activity of the lesions in JLS, but skin atrophy can give false-positive results.	4	D	90
4	A specialised US imaging, using standardised assessment and colour Doppler, may be a useful tool for assessing disease activity, extent of JLS and response to treatment.	4	D	100
5	All patients with JLS at diagnosis and during follow-up should be carefully evaluated with a complete joint examination, including the temporomandibular joint.	2a	C	100
6	MRI can be considered a useful tool to assess musculoskeletal involvement in JLS, especially when the lesion crosses the joint.	3	C	100
7	It is highly recommended that all patients with JLS involving face and head, with or without signs of neurological involvement, have an MRI of the head at the time of the diagnosis.	3	C	90
8	All patients with JLS involving face and head should undergo an orthodontic and maxillofacial evaluation at diagnosis and during follow-up.	2b	B	90
9	Ophthalmological assessment, including screening for uveitis, is recommended at diagnosis for every patient with JLS, especially in those with skin lesions on the face and scalp.	2a	C	100
10	Ophthalmological follow-up, including screening for uveitis, should be considered for every patient with JLS, especially in those with skin lesions on the face and scalp.	3	C	100

JLS, juvenile localised scleroderma; L, level of evidence; LoSCAT, Localized Scleroderma Cutaneous Assessment Tool; LoSDI, Localized Scleroderma Skin Damage Index; LoSSI, Localized Scleroderma Skin Severity Index; S, strength of recommendation; US, ultrasound.

meetings on March 2014 in Genova (Italy) and on March 2015 in Barcelona (Spain). At both meeting, a non-voting expert (SJV) facilitated the process. Recommendations were accepted when ≥80% of the experts agreed.

RESULTS

The literature search yielded 1550 papers; after the application of inclusion/exclusion criteria, title/abstract and full-text screening, 53 papers (26 for assessment and 27 for treatment) were selected and sent to the expert committee for validity assessment. Following a consensus-based methodology, the scleroderma working group of SHARE formulated 22 recommendations for the management of JLS. In total, 1 overarching principle, 10 recommendations on assessment and 6 on therapy were accepted with ≥80% agreement among the experts. Topics include assessment of skin, extracutaneous involvement and treatment suggestions at disease onset and in refractory disease.

We briefly describe the recommendations with corresponding supporting literature. Tables 1 and 2 summarise the recommendations for JLS, their levels of evidence, recommendation strength and percentage of agreement between experts. Of note, two recommendations derive from randomised controlled trials (level of evidence 1b, strength of evidence A), while three derive from expert opinions (level of evidence 4, strength of evidence D).

Overarching principle

JLS includes a group of disorders whose manifestations are confined to the skin and subdermal tissues and, with rare exceptions, do not affect internal organs. The most widely used classification includes five subtypes: circumscribed morphoea, linear scleroderma, generalised morphoea, pansclerotic morphoea, and the mixed subtype where a combination of two or more of the previous subtypes is present.[2] It is a rare condition in children as the incidence is 3.4 cases per million children per year, the vast majority represented by the linear subtype.[6] The female to male ratio of JLS is 2.4:1, the mean age at onset is approximately 7.3 years,[7] although the disease can start as early as at birth.[8] The severity of the disease varies widely from isolated plaques to generalised morphoea, and to extensive linear lesions involving limbs, trunk and/or the face and head.[9]

Given the rarity of the disease, the expert group agreed that patients with suspected JLS should be referred to a specialised paediatric rheumatology centre for clinical assessment and treatment (table 1).

Assessment of skin lesions

The assessment of disease activity is crucial in patients with JLS. At the time of diagnosis and during follow-up, it is fundamental to determine whether a lesion is active in order to establish an appropriate treatment regimen. Indeed, quantifying the activity of specific lesions is important in order to evaluate the response

Table 2 Recommendations regarding treatment

	L	S	Agreement (%)
Systemic corticosteroids may be useful in the active inflammatory phase of JLS. At the same time as starting systemic corticosteroids, MTX or an alternative DMARD should be started.	2b	C	100
All patients with active, potentially disfiguring or disabling forms of JLS should be treated with oral or subcutaneous methotrexate at 15 mg/m²/week.	1b	A	100
If acceptable clinical improvement is achieved, methotrexate should be maintained for at least 12 months before tapering.	3	C	100
Mycophenolate mofetil may be used to treat severe JLS or MTX-refractory or MTX-intolerant patients.	2a	B	100
Medium-dose UVA1 phototherapy may be used to improve skin softness in isolated (circumscribed) morphoea lesions.	1b	A	100
Topical imiquimod may be used to decrease skin thickening of circumscribed morphoea.	3	C	100

DMARD, disease-modifying antirheumatic drug; JLS, juvenile localised scleroderma; L, level of evidence; MTX, methotrexate; S, strength of recommendation; UVA1, ultraviolet A1.

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to therapy. As for disease activity and severity, the experts agreed on using both multiparametric scoring systems and instrumental techniques (table 1).

LoSCAT (Localized Scleroderma Cutaneous Assessment Tool) is a scoring system that includes a Skin Severity Index (LoSSI) and a Skin Damage Index (LoSDI).[10 11] LoSSI is a validated clinical instrument that allows to assess activity and severity of JLS lesions. Indeed, it correlates well with disease activity evaluated by clinicians.[12] LoSSI includes four domains (body surface area involvement, degree of erythema, skin thickness and appearance of new lesion or old lesion extension), each one graded from 0 to 3, in 18 anatomic sites.[10] LoSDI assesses damage by a similar scoring system. It includes three domains: skin atrophy, subcutaneous tissue loss and hypo-hyperpigmentation.[11] Although this method does not evaluate the real size of the lesions, it can be performed by physicians in daily practice without the need for special equipment.

Infrared thermography (IT) is a non-invasive technique that detects infrared radiation and provides an image of the temperature distribution across the body surface.[13] IT has been shown to be of value in the detection of active lesions with high sensitivity (92%) but moderate specificity (68%).[13] False-positive results are related to the fact that old lesions lead to marked atrophy of skin, subcutaneous fat and muscle, with increased heat conduction from deeper tissues.

High-frequency ultrasound can detect several abnormalities such as increased blood flow related to inflammation as well as increased echogenicity due to fibrosis and loss of subcutaneous fat.[14 15] The main limits of this tool are its operator dependency and the lack of standardisation.

Assessment of extracutaneous involvement

Although cutaneous and subcutaneous involvement is prominent, almost 20% of patients with JLS present extracutaneous manifestations[16] which are more frequent in patients with linear scleroderma and consist essentially of arthritis, neurological findings or other autoimmune conditions. Based on published data and clinical experience, the experts approved six recommendations regarding the assessment and monitoring of the extracutaneous manifestations of JLS.

Articular involvement is the most frequent extracutaneous feature being present in up to 19% of patients.[16] It can manifest with limited range of joint motion from contractures and/or arthritis.

Articular involvement is more common in children with the linear subtype, but it can be present in any subtype of JLS.[16] Therefore, all patients with JLS should be evaluated with a comprehensive joint examination at diagnosis and during follow-up. Joint symptoms are more common in patients with linear scleroderma and the affected joint does not always correlate with the site of the cutaneous lesion. Children with JLS who develop arthritis often have positive rheumatoid factor, and sometimes an elevated erythrocyte sedimentation rate.[7] A few studies, conducted mainly in adults,[17 18] reported a positive correlation between MRI and clinical findings of arthritis, especially during treatment. In addition to the literature evidence, the expert panel reported a positive experience in using this non-invasive tool to assess musculoskeletal involvement in JLS.

Central nervous system (CNS) involvement, although rare, has been reported in children with JLS, especially in those with linear scleroderma of the face and scalp.[19] The most frequent signs and symptoms are seizures and headache, although behavioural changes and learning disabilities have been also described.[16 20] Abnormalities on MRI, such as calcifications, white matter changes and vascular malformations or vasculitis, have also been reported.[21] Considering that most of these changes have been reported in the linear scleroderma of the face/head, it is mandatory to perform an MRI of the head in every patient with facial/scalp lesions. The lesions may occur distant to the skin lesions and do not apparently represent a skin down to deep tissue full thickness pathology. These patients should also be screened for ocular abnormalities[16] as literature shows a correlation between ophthalmological and neurological involvement in patients with linear forms.[22] Among the ocular manifestations, anterior uveitis is the most frequent one although there can be direct involvement of the eye, eyelid, eyelashes and orbit with the JLS lesions. Being usually asymptomatic, an ophthalmological screening is recommended at the time of diagnosis and during follow-up.

Indeed, since linear scleroderma of the face is significantly associated with odontostomatologic abnormalities,[23] an orthodontic and maxillofacial evaluation at diagnosis and during follow-up is recommended. Joint approaches to treatment may be needed, including with plastic surgery input, when there are severe wasting of facial fat compartments or in the linear scalp lesions. A comprehensive review on the most recent advances on monitoring and treatment of JLS has been recently published.[24]

Treatment

Over the years, many treatments have been tried for JLS[24] frequently without significant evidence base. Management decisions should be based on the particular subtype of disease, the site of lesions and on the degree of activity.

Most recent reported data show effectiveness of systemic corticosteroids in association with methotrexate (MTX) in patients with active JLS, particularly in progressive linear scleroderma and generalised or pansclerotic morphoea. Experience with steroids for treatment of active disease in children is reported in many papers, mainly in combination with MTX.[25 26] Literature evidence suggests that systemic corticosteroids are effective and well tolerated in the active phase of the disease and this was confirmed by the expert panel.[27] Data from the literature mainly suggest two administration regimens: oral prednisone at a dosage of 1–2 mg/kg/day for a period of 2–3 months with subsequent gradual tapering,[28] or pulsed high-dose intravenous methylprednisolone (30 mg/kg) with various administration schedules.[25 26] As far as the preferred administration route and dosage is concerned, no agreement has been achieved by the expert committee, therefore both alternatives are accepted. In the future, comparative trials of the two regimes could be considered.

As for the disease-modifying antirheumatic drugs that should be started in combination with corticosteroids, experts recommend MTX as first-step treatment. The only randomised double-blind placebo-controlled trial published to date clearly shows the safety and efficacy of oral MTX in the treatment of JLS, initially in combination with corticosteroids.[28] A weekly regimen of 15 mg/m^2 MTX as single oral or subcutaneous dose is recommended. During the first 3 months of therapy, a course of corticosteroids, namely prednisone, should be used as adjunctive 'bridge therapy'.[28] Prolonged remission off medication is more likely to occur in patients treated for more than 12 months after achieving clinical remission on medication.[29 30] Therefore, once an acceptable clinical improvement is achieved, MTX should be maintained for at least 12 months before tapering, although longer term treatments are also frequently used.

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As for safety, several reports show that low-dose MTX is safe and well tolerated in the paediatric population,[25–30] with a low rate of non-severe side effects including nausea, headache and transient hepatotoxicity.[26 28 30]

If MTX is ineffective or the disease relapses after a period of clinical remission (ie, cutaneous disease progression or severe extracutaneous manifestations) or in the case of MTX-intolerant patients, mycophenolate mofetil (MMF) at a dose of 500–1000 mg/m^2 may be used, despite that lack of good evidence in the literature.[31] A retrospective study on efficacy of MMF, mostly in combination with MTX, in severe refractory JLS has shown clinical improvement in all patients and a good safety profile.[31] More trials on the safety and efficacy of MMF in a larger paediatric population with localised scleroderma are needed.

Circumscribed morphoea is generally of cosmetic concern only and should be treated with topical treatment. Some studies report efficacy of imiquimod (IMQ) in decreasing the skin thickening of isolated plaques of circumscribed morphoea.[32 33] IMQ is a novel immunomodulator which is effective in the treatment of keloids, genital warts and basal cell skin cancers. One of its modes of action is to upregulate a variety of cytokines including interferon α and γ. These interferons are capable of inhibiting collagen production by fibroblasts, likely by downregulating the production of transforming growth factor beta.[34 35] Although published literature includes mainly adult data in low numbers of patients,[33] IMQ appears to be safe in the paediatric population and despite limited evidence, the expert panel suggested its use in selected non-progressive or extended forms of JLS, although a formal trial is also recommended.

Phototherapy with ultraviolet (UV) light represents another possible therapeutic choice for JLS[36 37] although data on its use in children are scarce. Medium-dose UVA1 therapy seems to be effective in improving skin softness and reducing skin thickness with a good safety profile in adults with localised scleroderma.[36–38] Limitations for the use of phototherapy in children are the need for prolonged maintenance therapy, leading to a high cumulative dosage of irradiation, and the increased risk of potential long-term effects such as skin ageing and carcinogenesis.[39]

Although there are, to date, no published trials of biologics or combination treatments, surveys of clinical practice demonstrate that tacrolimus, cyclophosphamide and a number of biologics (including tumour necrosis factor or interleukin-6 inhibitors) are being used in some patients for resistant or CNS disease.[40–43] There is also no high-level evidence regarding when to stop MTX or other immunosuppressive treatments. The expert panel suggested considering the withdrawal of MTX (or alternative disease-modifying drug) once the patient is in remission and off steroids for at least 1 year.

Based on consensus recommendations, a flow chart was proposed for JLS treatment (figure 1).

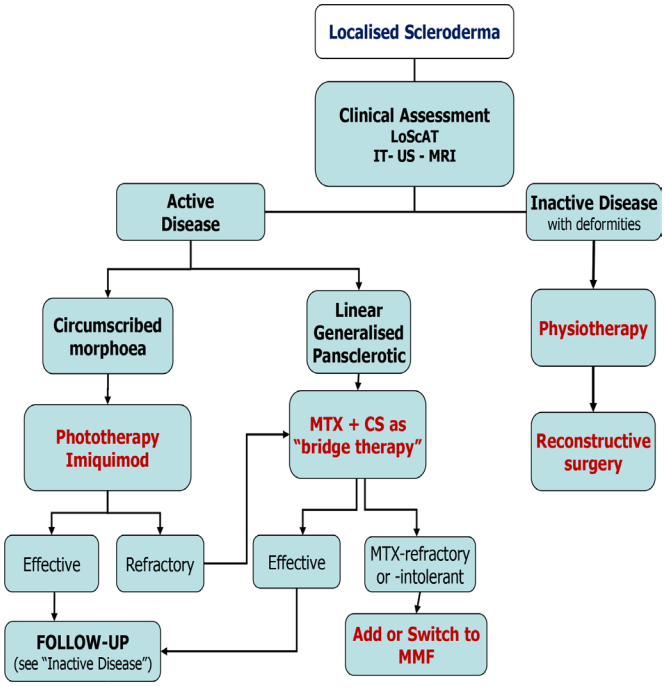

Figure 1 Flow chart for the treatment of newly diagnosed or refractory patients with juvenile localised scleroderma according to the clinical subtype. CS, corticosteroid; IT, infrared thermography; LoSCAT, Localized Scleroderma Cutaneous Assessment Tool; MMF, mycophenolate mofetil; MTX, methotrexate; US, ultrasound.

DISCUSSION

The scleroderma working group of SHARE formulated a total of 22 recommendations for the management of JLS, based on a systematic literature review and consensus procedure.

Topics include assessment of skin lesions and extracutaneous involvement, and the use of topical and systemic treatment options.

In total, 1 overarching principle, 10 recommendations on assessment and 6 on therapy were accepted with ≥80% agreement among the experts.

Close monitoring of patients' disease status and well-being by an experienced multidisciplinary and interdisciplinary team with expertise in localised scleroderma is essential for a good clinical outcome.

As in patients with idiopathic inflammatory myopathies or other rare connective tissue diseases all experts agree on the importance of managing JLS in specialised centres.[44] As with all significant rare disorders, concentrating care in a few centres gives rise to a larger physician experience. In addition, European and international sharing of patients in studies provides evidence to improve standards of care. An important message from both the literature and the experience of experts is the requirement of a global evaluation of patients with JLS, focusing attention on the skin lesions and on possible extracutaneous involvement, which even though are rare can also be severe and potentially disabling. Validated scores for disease activity and damage are proposed in order to perform a structured assessment of outcome over time and to closely check their effect on the growth in children.

Recent evidence highlights the importance of treating skin disease aggressively as it is associated with high morbidity both physically and psychologically. Long-term follow-up studies are warranted to clarify complication risks and predictors of poor outcome. Given the disease rarity, international collaboration is crucial to recruit sufficient patients for future clinical trials with both current and innovative drugs.

To conclude, this SHARE initiative is based on expert opinion informed by the best available evidence and provides recommendations for the diagnosis and treatment of patients with JLS, along with other paediatric rheumatic diseases, with a view to improving their outcome in Europe. We anticipate that these guidelines will likely be adopted by physicians caring for patients with JLS outside Europe.

It will now be important to broaden discussion and test the reliability of these recommendations to the wider scientific community and to the patients.

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EXTENDED REPORT

Consensus-based recommendations for the management of juvenile dermatomyositis

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ABSTRACT

Background In 2012, a European initiative called *S*ingle *H*ub and *A*ccess point for pediatric *R*heumatology in *E*urope (SHARE) was launched to optimise and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. Juvenile dermatomyositis (JDM) is a rare disease within the group of *paediatric rheumatic diseases* (PRDs) and can lead to significant morbidity. Evidence-based guidelines are sparse and management is mostly based on physicians' experience. Consequently, treatment regimens differ throughout Europe.

Objectives To provide recommendations for diagnosis and treatment of JDM.

Methods Recommendations were developed by an evidence-informed consensus process using the European League Against Rheumatism standard operating procedures. A committee was constituted, consisting of 19 experienced paediatric rheumatologists and 2 experts in paediatric exercise physiology and physical therapy, mainly from Europe. Recommendations derived from a validated systematic literature review were evaluated by an online survey and subsequently discussed at two consensus meetings using nominal group technique. Recommendations were accepted if >80% agreement was reached.

Results In total, 7 overarching principles, 33 recommendations on diagnosis and 19 recommendations on therapy were accepted with >80% agreement among experts. Topics covered include assessment of skin, muscle and major organ involvement and suggested treatment pathways.

Conclusions The SHARE initiative aims to identify best practices for treatment of patients suffering from PRD. Within this remit, recommendations for the diagnosis and treatment of JDM have been formulated by an evidence-informed consensus process to produce a standard of care for patients with JDM throughout Europe.

INTRODUCTION

In 2012, *S*ingle *H*ub and *A*ccess point for pediatric *R*heumatology in *E*urope (SHARE) was launched with the aim of optimising and disseminating diagnostic and management regimens for children and young people with rheumatic diseases. This includes juvenile dermatomyositis (JDM); the focus of this paper. Clear recommendations can help clinicians in the care of patients with JDM as no international consensus regarding diagnosis and treatment is currently available and management therefore varies.

METHODS

A committee of 19 experts in paediatric rheumatology, 2 experts in exercise physiology and physical therapy was established to develop recommendations for JDM based on consensus, but evidence informed, using the European League Against Rheumatism (EULAR) standard operating procedures for developing best practice.[1 2]

Systematic literature search

The electronic databases PubMed/MEDLINE, Embase and Cochrane were searched twice for eligible articles in June 2013 and subsequently in February 2015. All synonyms of JDM were searched in MeSH/Emtree terms, title and abstract. Reference tracking was performed in all included studies (full search strategy in online supplementary figure S1). Experts (FBE, LJMC, AvR-K) selected papers relevant to JDM investigations and/or treatment to be taken forward for validity assessment (inclusion and exclusion criteria shown in online supplementary figure S1). All full-text scored papers are listed in online supplementary list S1.

Validity assessment

A panel of experts (two per paper) independently assessed the methodological quality of papers meeting inclusion criteria (see online supplementary figure S1) and extracted data using predefined scoring forms for diagnostic[3] and therapeutic studies.[4] Disagreements were resolved by discussion or by the opinion of a third expert. Adapted classification tables for diagnostic,[5] therapeutic[1 6] and epidemiological studies[7] were used to determine the level of evidence and strength of each recommendation.

Establishment of recommendations

As part of the EULAR standard operating procedure, experts described the main results and conclusions of each paper, along with validity and level of evidence. These descriptions were collated by three experts (FBE, LJMC and AvR-K) and used to formulate provisional recommendations (N=65).

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A summary of the evidence was presented along with each provisional recommendation to the expert committee (n=21) in an online survey (with 100% response rate). Recommendations were revised according to responses and discussed at two sequential face-to-face consensus meetings in March 2014 (Genova, number of experts participating: N=13) and 2015 (Barcelona, number of experts participating: N=15), using Nominal Group Technique.[8] A non-voting expert (AR) facilitated the process. Recommendations were accepted when ≥80% of the experts agreed.

RESULTS

Literature review

The literature search yielded 3429 unique papers. After title/abstract and subsequent full-text screening, 115 articles met the inclusion criteria and were selected for quality scoring: 45 articles for therapy, 70 for diagnosis and 3 articles for both groups (detailed in online supplementary figure/list S1). An important manuscript detailing a randomised controlled trial involving treatment with prednisolone, methotrexate (MTX) and ciclosporin was published after the systematic review and consensus meetings, but before submission of this manuscript. With the results of this paper considered, the level of evidence of two recommendations in the therapy section was updated, but the phrasing was not changed.[9]

Recommendations

The following section describes recommendations with corresponding supporting literature. Tables 1–3 summarise the recommendations, their levels of evidence, recommendation strength and percentage of expert agreement for each. Of note, 39 out of the 59 recommendations accepted are based on expert opinion (level of evidence 4, a strength of evidence D). Recommendations not reaching ≥80% agreement are listed in online supplementary table T1 (N=6).

Overarching principles

JDM is the most common idiopathic inflammatory myopathy of childhood, but the incidence is very low; 2–4 cases per million children per year (table 1).[10] Standardisation of diagnostic tests and treatment regimens will enable collaborative research studies to increase knowledge of this rare disease.[11] JDM vasculopathy principally affects muscles and skin, but may affect other organs and cause constitutional symptoms. With early treatment, 30–50% of patients have the potential to reach remission within 2–3 years of disease onset with few complications and a mortality rate of <4%.[12–15] However, polycyclic or persistently active disease has been described in 41–60% of cases in recent cohort studies (depending on activity measures used) and complications like calcinosis, persistent muscle weakness, skin or muscle atrophy remain problematic.[12 14–19] Risk of lipodystrophy and calcinosis has been associated with greater duration of active disease and inadequate corticosteroid therapy.[15 17 20 21] Quality of life may be impaired compared with healthy controls[15] in both physical and psychosocial domains, requiring psychosocial support. In view of the rarity and seriousness of the condition, it was agreed that children with JDM should be cared for in centres with experience and expertise in this condition. Treatment goals include control of disease activity, prevention of organ damage and improvement in quality of life with participation in daily activities. Evaluation of treatment response (including measurement of disease activity or disease damage and monitoring adverse effects of immunosuppressive medication) is an important cornerstone of management.[22–24] Many standardised tools, developed primarily for research, are available for this, including the disease activity score (DAS) and myositis disease activity assessment tool.[25] It is recognised that registries provide useful resources to investigate rare disease such as JDM.[11] In order to better understand prognosis and enhance therapeutic development of this rare disease,

Table 1 Overarching principles for juvenile dermatomyositis (JDM)

	L	S	Agreement (%)
All children with suspected idiopathic inflammatory myopathies should be referred to a specialised centre.	4	D	100
High-risk patients need immediate/urgent referral to a specialised centre. High risk patients are defined by A. Severe disability, defined by inability to get off bed B. CMAS score <15, or MMT8 score <30 C. Presence of aspiration or dysphagia (to the point of inability to swallow) D. Gastrointestinal vasculitis (as determined by imaging or presence of bloody stools) E. Myocarditis F. Parenchymal lung disease G. Central nervous system disease (defined as decreased level of consciousness or seizures) H. Skin ulceration I. Requirement for intensive care unit management J. Age <1 year	4	D	100
For JDM, patient-/parent-reported outcome measures are helpful when assessing disease activity and should be used at diagnosis and during disease monitoring.	4	D	100
Validated tools should be used to measure health status, for example, the Childhood Health Assessment Questionnaire, patient/parent visual analogue scale, Childhood Health Questionnaire, Juvenile Dermatomyositis Multi-dimensional Assessment Report.	4	D	82
All children with JDM should have disease activity (muscle, skin, major organ) assessed regularly in a standardised way, using tools such as the Disease Activity Score.	4	D	100
All children with JDM should have disease damage assessed at least yearly using a standardised disease damage measure, such as the Myositis Damage Index.	4	D	100
All patients with JDM should have the opportunity to be registered within a research registry/repository, for example, the Euromyositis registry.	4	D	100

Agreement indicates percentage of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of randomised controlled trial; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4 expert opinion; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; CMAS, Childhood Myositis Assessment Scale; D, based on level 4 or extrapolated from level 3 or 4 expert opinion; L, level of evidence; MMT, Manual Muscle Test; S, strength of recommendation;

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Table 2 Recommendations regarding diagnosis

	L	S	Agreement (%)
(a) General recommendations			
In the absence of cutaneous signs and/or failure to respond as expected to therapy, alternative diagnoses should be considered including metabolic or mitochondrial myopathies and dystrophies.	4	D	100
In every patient in whom a diagnosis of JDM is considered, the following list of investigations should be considered: A. Muscle enzymes—including creatinine phosphokinase (CPK), LDH, AST (SGOT), ALT (SGPT), adolase (if available) B. Full blood count and blood film C. ESR (or plasma viscosity) and CRP D. Myositis-specific and myositis-associated antibodies E. Renal function and liver function tests F. Infection screen (for differential diagnosis) G. Investigations for alternative systemic causes of myopathy including endocrine disorders (especially thyroid function), electrolyte disturbances, vitamin D deficiency H. Further tests for metabolic/mitochondrial myopathies (especially in the absence of rash/atypical presentation) I. Urine dipstick (with further evaluation if positive for protein) J. Nailfold capillaroscopy K. Echocardiogram and ECG L. Pulmonary function tests (chest X-ray and HRCT if concern) M. MRI of muscles (+quantitative ultrasound) N. EMG (particularly if suspicion of neuropathy/disorder of neuromuscular junction) O. Muscle biopsy (especially in the absence of rash/atypical presentation) P. MRI brain if neurological involvement suspected Q. Abdominal ultrasound scan	4	D	94
(b) Specific recommendations			
Assessment of muscle involvement			
Both muscle strength and function should be tested at diagnosis and follow up by formal validated measures, such as the MMT8 and the CMAS.	2a-3	B–C	100
MRI can be used to aid diagnosis of JDM.	2B	B	100
MRI can be used to help monitor disease activity.	2B	B	100
When used, MRI should be carried out by defined protocols that enhance detection of muscle inflammation, such as T2 weighted/STIR sequences.	3	C	100
MRI should be interpreted by an expert radiologist.	4	D	100
A muscle biopsy should be done in all cases where the presentation of JDM is atypical; in particular in the absence of rash/skin signs.	4	D	100
If a muscle biopsy is performed for diagnosis of JDM, a standardised JDM biopsy score tool should be used to quantify severity of histological abnormalities.	2B	B	100
Expert histopathological opinion is required to define features of inflammation in JDM muscle biopsy.	4	D	100
When doing a muscle biopsy, there is insufficient evidence to recommend a needle biopsy as opposed to an open biopsy in children.	3	C	100
In cases where MRI or muscle biopsy is not possible, increased muscle echo intensity on muscle ultrasonography (when performed by an experienced sonographer) may be indicative of myositis.	2B	C	82
Swallow function should be formally assessed in every patient. The assessment may include a speech and language therapy assessment, video fluoroscopy/barium studies.	3	C	100
EMG or nerve conduction velocity should be considered to differentiate myopathy from neuropathy when diagnosis of JDM is uncertain.	4	D	100
EMG does not detect metabolic myopathies reliably and further workup is required if this diagnosis is suspected.	3	D	100
Assessment of skin involvement			
Assessment of nailfold capillaries should be used to aid diagnosis of JDM.	2	B	100
At time of diagnosis or disease flare, standardised nailfold capillaroscopy assessment is recommended. During follow-up, assessment of nailfold capillaries should be performed regularly.	3	C	100
A formal CAT should be used to aid diagnosis of JDM.	4	D	100
A formal CAT should be used to monitor skin disease activity over time.	2B	B	100
Skin tools may include the DAS (skin), MITAX (skin) or CAT.	4	D	100
Assessment of lung involvement			
All patients with JDM should have an assessment of lung involvement at time of diagnosis.	3	C	100
Assessment should include pulmonary function tests, including CO diffusion. If pulmonary function tests are indicative of interstitial lung disease, further investigations (CXR/ HRCT) are needed.	4	D	100
Assessment of cardiac involvement.			
All patients with JDM should have echocardiography and ECG at diagnosis.	4	D	94
Patients at particular risk of cardiac dysfunction should have repeated cardiac evaluation. Risk factors include hypertension, high disease activity 1 year post diagnosis, long-term high corticosteroid burden or chronic ongoing active disease.	2B	B	100
Assessment of calcinosis			
Calcinosis should be looked for in all patients with JDM.	4	D	94
Plain radiographs may be used for the evaluation of calcinosis.	3	C	100

Continued

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Table 2 Continued

	L	S	Agreement (%)
Autoantibodies and biomarkers			
We recommend use of muscle enzymes (CPK, LDH, AST) for diagnosis and disease monitoring in JDM, although it must be recognised muscle enzymes may be normal despite active disease.	4	D	100
Measurement of von Willebrand factor does not provide any additional information for diagnosis of JDM.	3	C	100
There is no significant diagnostic benefit gained from measurement of antinuclear antibody in JDM.	4	D	100
Measurement of myositis-specific autoantibodies (such as anti-TIF 1-γ (p155), anti-NXP2/(p140/MJ), anti-MDA5 and anti-SRP) should be considered, when available.	2A-3	B–C	100
In patients with overlap features, measurement of myositis-associated-antibodies such as anti-PmScl, anti-U1-RNP, anti-La ('SSB'), anti-Ro ('SSA') and anti-Sm may be helpful to clarify the diagnosis.	4	D	100
Further validation studies are recommended to define the use of more sensitive biomarkers in JDM.	4	D	100

Agreement indicates percentage of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of randomised controlled trial; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4 expert opinion; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, based on level 3 or extrapolated from level 1 or 2; CAT, Cutaneous Assessment Tool; CMAS, Childhood Myositis Assessment Scale; CO, carbon monoxide; CRP, C-reactive protein; CXR, chest X-ray; D, based on level 4 or extrapolated from level 3 or 4 expert opinion; EMG, electromyogram; ESR, erythrocyte sedimentation rate; HRCT, high-resolution computed tomography; L, level of evidence; LDH, lactate dehydrogenase; MITAX, myositis intention to treat activity index; MMT, Manual Muscle Test; RNP, anti-ribonuclear protein; S, strength of recommendation; SGOT, Serum Glutamic-Oxaloacetic Transaminase; SGPT, Serum Glutamic-Pyruvic Transaminase; SRP, signal recognition particle; SSA, Ro antibodies; SSB, Sjögren's syndrome type B antibodies; STIR, Short-TI Inversion Recovery.

Table 3 Recommendations regarding treatment

	L	S	Agreement (%)
Sun protection, including the routine use of sunblock on sun-exposed areas should be encouraged for patients with JDM.	4	D	100
When treating patients with JDM, it is particularly important to have a physiotherapist and a specialist nurse actively involved as part of a multidisciplinary team.	4	D	100
Treatment of JDM should include a safe and appropriate exercise programme, monitored by a physiotherapist.	4	D	100
We recommend the induction regimen for treatment of new onset patients with JDM to be based on high dose of corticosteroids (oral or intravenous) combined with MTX.	1B	A	100
High-dose corticosteroids should be administered systemically either orally or intravenously in moderate–severe JDM.	2A	B	100
High-dose corticosteroids should be administered intravenously if there are concerns about absorption.	3	C	100
Corticosteroid dose should be weaned as the patient shows clinical improvement.	4	D	100
Addition of MTX or ciclosporin A leads to better disease control than prednisolone alone; safety profiles favour the combination of methotrexate and prednisolone.	1B	A	100
MTX should be started at a dose of 15–20 mg/m^2/week (max absolute dose of 40 mg /week) preferably administered subcutaneously at disease onset.	4	D	100
If a newly diagnosed patient has inadequate response to treatment, intensification of treatment should be considered within the first 12 weeks, after consultation with an expert centre.	4	D	100
Intravenous immunoglobulin may be a useful adjunct for resistant disease, particularly when skin features are prominent.	2B-4	C	100
MMF may be a useful therapy for muscle and skin disease (including calcinosis).	3	C	100
Ongoing skin disease reflects ongoing systemic disease and therefore should be treated by increasing systemic immunosuppression. Topical tacrolimus (0.1%)/topical steroids may help localised skin disease, particularly for symptomatic redness or itching.	4	D	100
In patients who are intolerant to methotrexate, change to another DMARD, including ciclosporin A or MMF.	3	C	100
For patients with severe disease (such as major organ involvement/extensive ulcerative skin disease), addition of intravenous cyclophosphamide should be considered.	3	C	100
B cell depletion therapy (rituximab) can be considered as an adjunctive therapy for those with refractory disease. Clinicians should be aware that rituximab can take up to 26 weeks to work.	1B	D	100
Anti-TNF therapies can be considered in refractory disease; infliximab or adalimumab are favoured over etanercept.	3	D	92
In the presence of developing or established calcinosis, intensification of immunosuppressive therapy should be considered.	3	C	100
There is no high-level evidence of when to stop therapy; however, consideration may be given to withdrawing treatment if a patient has been off steroids and in remission on methotrexate (or alternative DMARD) for a minimum of 1 year.	4	D	100

Agreement indicates percentage of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of randomised controlled trial; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4 expert opinion; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion; DMARD, disease-modifying antirheumatic drug; JDM, juvenile dermatomyositis; L, level of evidence; MMF, mycophenolate mofetil; MTX, methotrexate; S, strength of recommendation; TNF, tumour necrosis factor.

the expert group found it important to recommend that all patients JDM should have the opportunity to participate in a research registry.

Recommendations regarding diagnosis

Diagnostic criteria for dermatomyositis, established by Bohan and Peter in 1975, include five items: characteristic skin rash,

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proximal muscle weakness, raised muscle enzymes, myopathic changes on electromyogram (EMG) and typical muscle biopsy (table 2).[26] These are currently being revised through the International Myositis Classification Criteria Project.[27] Current practice reveals the necessity of broadening diagnostic criteria by incorporating new techniques, such us MRI and ultrasound, and the significance of skin disease in JDM.[14 15 21 28 29] The expert group suggested a non-exhaustive list of investigations for consideration in every patient in whom the diagnosis of JDM is suspected. More specific recommendations have also been established.

Assessment of muscle disease

Muscle strength should be formally tested using validated measures of muscle testing such as the Childhood Myositis Assessment Scale (CMAS) and Manual Muscle Test (MMT). Both tools have been validated as reliable and useful tests to assess muscle strength at diagnosis and follow-up.[30–33] They are important outcome measurements in clinical trials and form part of the Paediatric Rheumatology INternational Trials Organization (PRINTO) remission criteria.[34] Some of the CMAS manoeuvres are age dependent. It has been shown that healthy children up to 9 years do not always achieve the maximum CMAS score of 52, hence, definition of active disease/remission should include a lower threshold in younger children.[35 36]

MRI is a reliable tool to assess inflammation in muscle at time of diagnosis and can also help to differentiate active and inactive disease during follow-up.[37] Protocols that enhance detection of muscle inflammation, such as T2-weighted (fat-suppressed) imaging techniques,[38] should be used. An expert radiologist should evaluate MRI findings.[39]

Surveys and recent cohort studies demonstrate increasing use of MRI over time (26–89.9%) as a diagnostic modality in contrast to decreasing use of muscle biopsy (36–65%) and EMG (7.6–55.5%)[14 15 21 28 29 40] The expert group recommend EMG or nerve conduction velocity only when diagnosis is uncertain. Of note, EMG does not reliably detect metabolic myopathies.[41]

The expert group advises biopsy when presentation is atypical or diagnosis is in doubt. Use of a standardised JDM biopsy score tool to quantify severity of histological abnormalities is recommended.[42] Different markers have been suggested to typify muscle inflammation in patients with JDM, like major histocompatibility complex (MHC) class I, vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), CD59 and toll-like receptor (TLR),[43–48] but these need further validation. Expert histopathological opinion is required to define use of these markers for diagnosis of JDM based on muscle biopsy findings. The literature suggests that needle biopsy is a safe and cost-effective alternative to open biopsy in adult patients.[49] However, this has not been evaluated sufficiently in children to result in a recommendation.

Ultrasonography has been found in small patients cohorts (7–10 patients) to be a useful tool for myositis.[50 51] The expert group suggests that when MRI or muscle biopsy is not possible muscle ultrasonography may be an alternative to assess myositis activity.

The literature suggests that swallowing dysfunction, including silent aspiration, is under-recognised and not always predicted by generalised muscle weakness.[52] The expert group recommend that patients at risk of swallowing difficulties (eg, those presenting with nasal speech or coughing during swallowing) should have an objective assessment based on local experience (speech and language therapy assessment, video fluoroscopy/barium studies).

Assessment of skin disease

The expert group recommend use of a cutaneous assessment tool (CAT), including nailfold capillaroscopy to detect periungual capillary changes, as part of assessment of JDM skin activity at diagnosis and follow-up. This can be done in clinic with the aid of magnification using an otoscope, ophthalmoscope or dermatoscope, or defined by formal capillaroscopy. Evidence suggests that nailfold capillary density is a sensitive measure of skin and muscle disease activity.[53–58] The importance of residual skin changes in JDM is increasingly recognised, with persistent capillary abnormalities and Gottron's papules at 6 months being associated with longer time to remission.[16] The expert group therefore recommend that follow-up of patients with JDM should include use of a CAT. Different tools are available, including the DAS (skin), Myositis Intention to Treat Activity IndeX (MITAX, skin), CAT, Dermatomyositis Skin Severity Index or Cutaneous Dermatomyositis Disease Area and Severity Index; the last two less frequently used in children. There is currently insufficient evidence that any one tool is superior to the other.[59–61]

Assessment of JDM-associated lung disease

Lung involvement (interstitial lung disease (ILD)) is present in only ~8% of patients, and often asymptomatic, but assessment is important since ILD is a significant cause of morbidity and mortality.[62] The expert group determined that all children should have assessment of lung involvement at time of diagnosis by pulmonary function tests, including carbon monoxide (CO) diffusion capacity.[63 64] Further testing is necessary in those with an abnormal restrictive pattern, preferably in collaboration with a paediatric pulmonologist. The performance of pulmonary function tests can be difficult in very young children and can also be affected by general muscle weakness. High-resolution CT is a non-invasive and sensitive test for detecting ILD in JDM, but radiation risk associated with repeated CT scan must be considered.[63] There is insufficient evidence to advise on frequency of assessment during follow-up, but physicians should be aware of the long-term risk of lung involvement especially in those with a high myositis damage index (MDI) score[62] and a regular assessment of lung function may be prudent in patients that have positive anti-RNA synthetase antibodies.[64]

Assessment of JDM-associated cardiac disease

Understanding of cardiac manifestations in JDM is limited. One long-term complication is hypertension due to steroid treatment.[65] Case studies report the presence of pericarditis, endocarditis and cardiac arrhythmias.[66 67] Recent evidence using echocardiography has detected systolic and diastolic dysfunction, particularly in patients with high long-term organ damage scores (MDI, follow-up) and high early skin (but not muscle) disease activity (DAS skin, year 1). Notably, most patients were asymptomatic. The authors of the study suggest that vasculopathy in the myocardium resembles vasculopathy in the skin.[65] The long-term clinical consequences of abnormal echocardiographic findings in asymptomatic patients with JDM are unclear. The expert group recommends cardiac evaluation by ECG and echocardiography for all patients. Repeated cardiac evaluation should be considered in patients with high risk of cardiac involvement; risk factors include hypertension, high disease activity 1 year post diagnosis, long-term high corticosteroid burden or chronic ongoing active disease.[65] Echocardiac changes are recognised even when patients are in clinical remission[65 68] and thus long-term cardiac evaluation should be considered for patients at high risk. There is currently insufficient evidence to advise on frequency and duration of monitoring.

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Assessment of calcinosis

Calcinosis is a well-recognised complication in patients with JDM, often occurring later in disease course, on average 2.9 years after disease onset.[18] The expert group recommends actively looking for calcinosis by manual palpation, with the use of plain radiographs where needed. CT has been found to have no additional benefit over radiographs for detecting calcinosis.[69]

Biomarkers and autoantibodies

Muscle enzymes are not always elevated at diagnosis of JDM and are poorly responsive to changing disease activity.[70–72] Consensus processes have demonstrated differences in opinion regarding inclusion of muscle enzymes as a core set measure of activity. The International Myositis Association and Clinical Studies Group (IMACS) core set includes muscle enzymes, but the PRINTO core set excludes muscle enzymes due to their poor statistical performance.[73 74] Despite these limitations, muscle enzymes are easily accessible and practice surveys suggest that the enzymes are used in routine care at diagnosis and during follow-up.[14 15 21 28 29] The expert group recommends measurement of all listed enzymes at diagnosis (table 2) and follow-up as one of them may be elevated in the presence of a normal creatinine phosphokinase (CPK). From current literature, there is no evidence that the von Willebrand factor provides additional information compared with muscle enzymes.[75] Several markers of immunological activation appear to correlate with disease activity or potentially with worse disease outcome in JDM, but further studies are needed to determine their sensitivity, like interferon (IFN)-I chemokine signatures[76–78] and neopterin.[79]

Antinuclear antibodies are frequently positive in patients with JDM (prevalence varies through different populations), but no diagnostic value has been established.[80] Increasing evidence supports association between serotype and clinical phenotype.[81] Myositis-specific autoantibodies target either nuclear or cytoplasmic components involved in gene transcription, protein translocation and antiviral responses. The literature suggests that the presence of anti-p155 (anti-TIF1γ) myositis-associated antibodies (MAA) predicts worse cutaneous involvement, anti-p140 (also known as NXP-2 or MJ), predicts calcinosis, severe disease course and persistent disease activity, and anti-MDA5 is associated with increased risk of skin and oral ulceration, arthritis, milder muscle disease and interstitial lung disease. The association with severe lung disease was most striking in Japanese patients. Anti-signal recognition particle (SRP) is associated with necrotising autoimmune myopathy.[20 82–90] The studies mentioned above provide control sera derived from adults and none of these autoantibodies have been validated to date in large patient cohorts. At the time of publication, there is insufficient evidence to recommend measurement of autoantibodies for risk stratification due to lack of validation and data in patients from different ethnicities. However, when available, measurement of myositis-specific antibodies or MAA may be helpful, but should be performed and validated in a laboratory with experience and expertise.

Therapy

Early and aggressive therapy may prevent or stabilise organ damage and disease complications like calcinosis, the latter being associated with significant morbidity due to pain and risk of infection (table 3).[14 15 21 71 91–94] JDM treatment is largely based on experience of the treating paediatric rheumatologist. Management is complex and warrants a multidisciplinary approach including physiotherapists, specialist nurses and paediatric rheumatologists, with other specialists, as needed, for example, cardiologist/pulmonologist. The mainstay of therapy is high-dose corticosteroid initially in combination with disease-modifying drugs like MTX or ciclosporin A (CsA).[71 95] Evidence for treatment is limited and often confined to small case-controlled studies, with the exception of two randomised controlled trials.[9 96] In 2010, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) reached consensus on treatment plans for moderately severe JDM for the first two months after diagnosis that include a combination of steroid (intravenous methylprednisolone followed by oral prednisolone or high-dose oral prednisolone alone) and MTX±intravenous immunoglobulin (IVIG).[97]

The only randomised controlled trial for newly diagnosed patients was performed by PRINTO from 2006 to 2011, comparing three commonly used protocols (prednisone alone vs combination of prednisone with either MTX or CsA). The combination of steroids and MTX had the best outcome for efficacy and safety.[9] In 2013, a randomised controlled trial was published for use of rituximab in refractory myositis, including JDM, in a delayed start design.[96] There was no statistically significant difference between treatment groups, but 83% of patients met the definition of improvement by trial completion. These data, with the ability to taper glucocorticoid therapy and good re-treatment response, suggest that rituximab may be useful in refractory cases of myositis.[98]

The expert group proposed recommendations for treatment of newly diagnosed patients and resistant disease. Treatment of refractory patients with or without calcinosis[15] is still a challenge. Treatments used for refractory disease include IVIG, cyclophosphamide, CsA, azathioprine, mycophenolate mofetil (MMF), hydroxychloroquine, tacrolimus, rituximab, infliximab and autologous stem cell transplantation.[9 96 98–112] No head-to-head or superiority trial has been carried out.

Published data suggest that early aggressive treatment may decrease incidence of calcinosis.[14 15 21 71 91–94] Established calcinosis may respond to treatment with bisphosphonates (pamidronate/alendronate), infliximab, abatacept, diltiazem, probenecid, intravenous immunoglobulins, intralesional steroids or surgical resection.[101 111 113–124] Evidence for individual treatments is limited to case reports, except infliximab, diltiazem and pamidronate (case series of five, four and three patients, respectively); therefore, no recommendation regarding a specific treatment of calcinosis was made.

Therapeutic trials are hampered by recruitment of sufficient numbers of patients with JDM, but also by limited tools or biomarkers to measure outcome. Currently, there is no uniform, simple and practical tool to evaluate improvement or inactive disease to guide individual treatment. PRINTO and IMACS have developed preliminary definitions of improvement (DoI) for use in clinical trials, which include multiple assessments of core set measures (CSMs). Although the CSMs used within DoIs differ slightly, PRINTO and IMACS both expect at least 20% improvement in three out of six CSMs with no more than one or two other core set measures getting worse and muscle strength not allowed to worsen.[74 125] These definitions and recommendations are best suited to clinical trials, with appropriate infrastructure, but are time consuming in clinical practice. In 2012, CARRA developed a single-consensus steroid taper plan, including when and how to stop steroids.[126] However, the SHARE expert group did not agree to a specific steroid-tapering regimen.

In 2012, PRINTO published criteria defining clinically inactive disease; necessitating fulfilment of three out of four variables from CPK ≤150 U/L, CMAS ≥48, MMT8 ≥78 and

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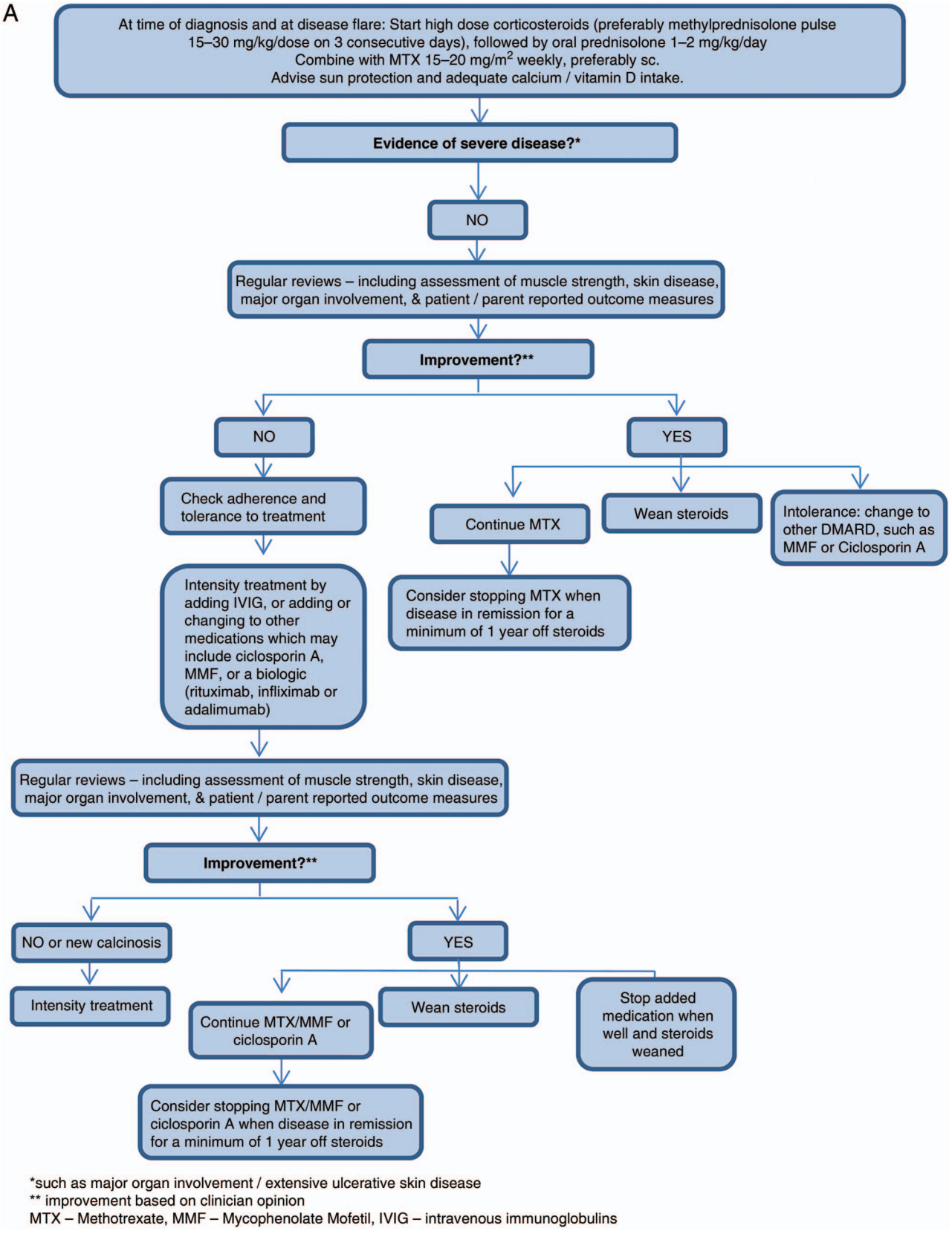
A
At time of diagnosis and at disease flare: Start high dose corticosteroids (preferably methylprednisolone pulse 15–30 mg/kg/dose on 3 consecutive days), followed by oral prednisolone 1–2 mg/kg/day
Combine with MTX 15–20 mg/m2 weekly, preferably sc.
Advise sun protection and adequate calcium / vitamin D intake.
Evidence of severe disease?*
NO
Regular reviews – including assessment of muscle strength, skin disease, major organ involvement, & patient / parent reported outcome measures
Improvement?**
NO
YES
Check adherence and tolerance to treatment
Continue MTX
Wean steroids
Intolerance: change to other DMARD, such as MMF or Ciclosporin A
Intensity treatment by adding IVIG, or adding or changing to other medications which may include ciclosporin A, MMF, or a biologic (rituximab, infliximab or adalimumab)
Consider stopping MTX when disease in remission for a minimum of 1 year off steroids
Regular reviews – including assessment of muscle strength, skin disease, major organ involvement, & patient / parent reported outcome measures
Improvement?**
NO or new calcinosis
YES
Intensity treatment
Continue MTX/MMF or ciclosporin A
Wean steroids
Stop added medication when well and steroids weaned
Consider stopping MTX/MMF or ciclosporin A when disease in remission for a minimum of 1 year off steroids
*such as major organ involvement / extensive ulcerative skin disease
** improvement based on clinician opinion
MTX – Methotrexate, MMF – Mycophenolate Mofetil, IVIG – intravenous immunoglobulins

Figure 1A Flow chart for the treatment of mild/moderate disease in newly diagnosed and refractory patients with juvenile dermatomyositis (JDM).

PGA score of overall disease activity ≤0.2.[34] These criteria are weighted towards muscle disease, and when tested in a Norwegian cohort[127] CPK was found not to differentiate well between active and inactive disease. When tested in a UK cohort, without PGA, there was a high incidence of skin disease, leading to the suggestion that PGA should be an essential criterion since it is the only measure that includes skin activity.[128] The expert group determined that treatment should be escalated if a patient has inadequate response to treatment, including isolated skin disease.

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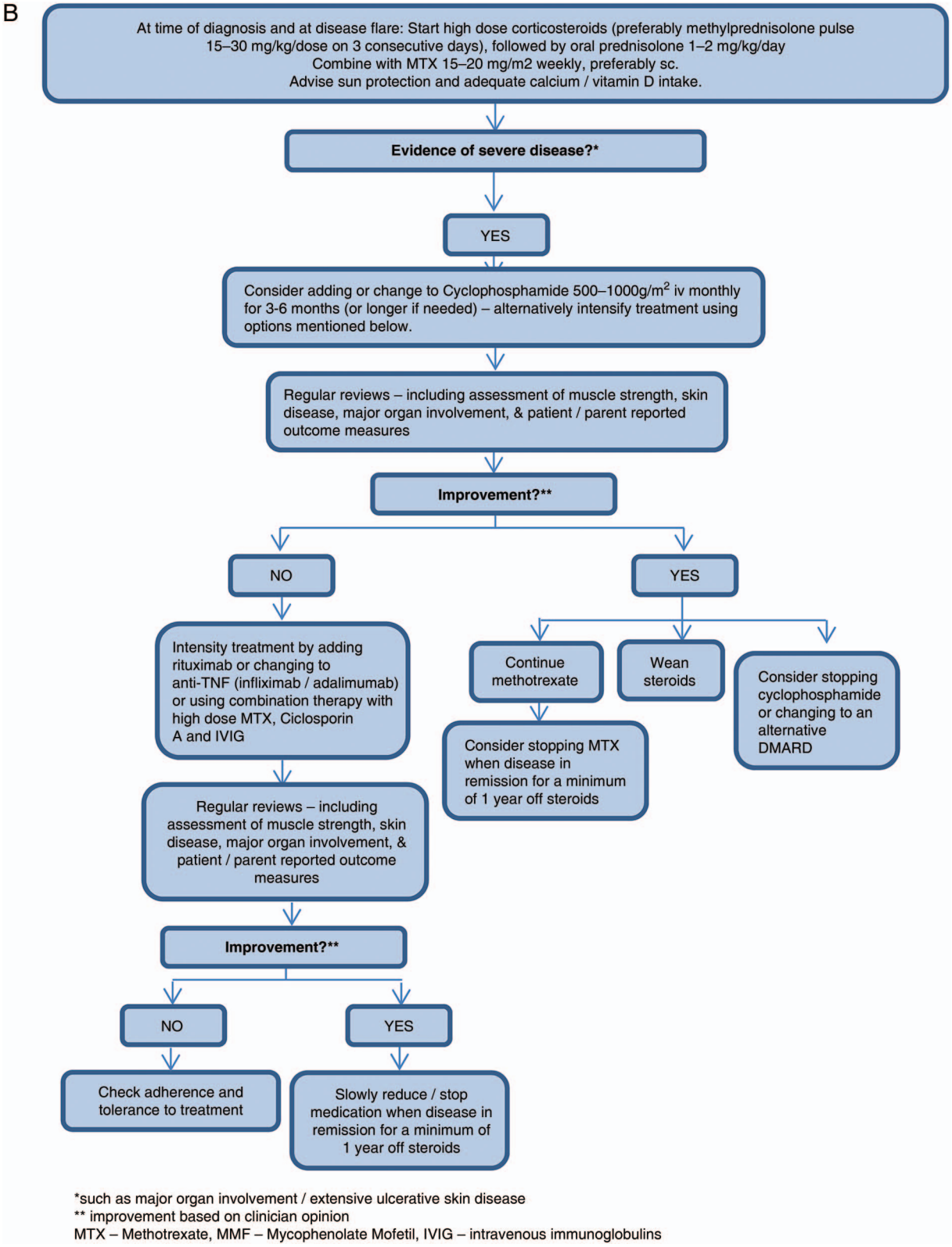
B
At time of diagnosis and at disease flare: Start high dose corticosteroids (preferably methylprednisolone pulse 15–30 mg/kg/dose on 3 consecutive days), followed by oral prednisolone 1–2 mg/kg/day
Combine with MTX 15–20 mg/m2 weekly, preferably sc.
Advise sun protection and adequate calcium / vitamin D intake.
Evidence of severe disease?*
YES
Consider adding or change to Cyclophosphamide 500–1000g/m2 iv monthly for 3-6 months (or longer if needed) – alternatively intensify treatment using options mentioned below.
Regular reviews – including assessment of muscle strength, skin disease, major organ involvement, & patient / parent reported outcome measures
Improvement?**
NO
YES
Intensity treatment by adding rituximab or changing to anti-TNF (infliximab / adalimumab) or using combination therapy with high dose MTX, Ciclosporin A and IVIG
Continue methotrexate
Wean steroids
Consider stopping cyclophosphamide or changing to an alternative DMARD
Consider stopping MTX when disease in remission for a minimum of 1 year off steroids
Regular reviews – including assessment of muscle strength, skin disease, major organ involvement, & patient / parent reported outcome measures
Improvement?**
NO
YES
Check adherence and tolerance to treatment
Slowly reduce / stop medication when disease in remission for a minimum of 1 year off steroids
*such as major organ involvement / extensive ulcerative skin disease
** improvement based on clinician opinion
MTX – Methotrexate, MMF – Mycophenolate Mofetil, IVIG – intravenous immunoglobulins

Figure 1B Flow chart for the treatment of severe disease in newly diagnosed and refractory patients with juvenile dermatomyositis (JDM).

There is no high-level evidence regarding when to stop immunosuppressive therapy. The expert group suggested considering the withdrawal of MTX (or alternative disease-modifying drug) once the patient is in remission and off steroids for a minimum of 1 year.

Based on consensus recommendations, a flow chart was established for JDM treatment (figure 1).

DISCUSSION

The JDM working group of SHARE formulated a total of 62 recommendations for the diagnosis and management of JDM, based on a systematic literature review and consensus procedure. In total, 7 overarching principles, 33 recommendations on diagnosis and 19 on therapy were accepted with >80% agreement among the experts. Topics include assessment of skin, muscle

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and major organ involvement and treatment suggestions at disease onset and in refractory disease.

Diagnostic criteria in JDM are under revision, but will need further adjustment as new outcome tools, especially autoantibodies and biomarkers, are being developed.

Close monitoring of patients' disease status and well-being by an experienced multidisciplinary team is essential for a good clinical outcome. Recent evidence highlights the importance of treating skin disease aggressively as it is associated with high morbidity. Long-term follow-up studies are warranted to clarify complication risks. Given the disease rarity, international collaboration is crucial to recruit sufficient patients. Validated scores for disease activity and damage are needed in order to perform a structured assessment of outcome. Disease activity and damage scores have been developed, principally for clinical trials, but may be challenging and time consuming to use in daily clinical practice.

To conclude, this SHARE initiative is based on expert opinion informed by the best available evidence and provides recommendations for the diagnosis and treatment of patients with JDM, along with other paediatric rheumatic diseases[129] with a view to improving the outcome for patients with JDM in Europe. It will now be important to broaden discussion and test acceptability of these to the wider community.

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2018 Update of the EULAR recommendations for the management of large vessel vasculitis

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ABSTRACT

Background Since the publication of the European League Against Rheumatism (EULAR) recommendations for the management of large vessel vasculitis (LVV) in 2009, several relevant randomised clinical trials and cohort analyses have been published, which have the potential to change clinical care and therefore supporting the need to update the original recommendations.

Methods Using EULAR standardised operating procedures for EULAR-endorsed recommendations, the EULAR task force undertook a systematic literature review and sought opinion from 20 experts from 13 countries. We modified existing recommendations and created new recommendations.

Results Three overarching principles and 10 recommendations were formulated. We recommend that a suspected diagnosis of LVV should be confirmed by imaging or histology. High dose glucocorticoid therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active giant cell arteritis (GCA) or Takayasu arteritis (TAK). We recommend adjunctive therapy in selected patients with GCA (refractory or relapsing disease, presence of an increased risk for glucocorticoid-related adverse events or complications) using tocilizumab. Methotrexate may be used as an alternative. Non-biological glucocorticoid-sparing agents should be given in combination with glucocorticoids in all patients with TAK and biological agents may be used in refractory or relapsing patients. We no longer recommend the routine use of antiplatelet or anticoagulant therapy for treatment of LVV unless it is indicated for other reasons.

Conclusions We have updated the recommendations for the management of LVV to facilitate the translation of current scientific evidence and expert opinion into better management and improved outcome of patients in clinical practice.

BACKGROUND

Rapid diagnosis and effective treatment are required in large vessel vasculitis (LVV) in order to treat symptoms, but more importantly, to reduce the risk of complications such as blindness in giant cell arteritis (GCA) and aortic aneurysm or vascular stenosis in GCA and Takayasu arteritis (TAK). In April 2008, the first recommendations of the European League against Rheumatism (EULAR) for managing LVV were published.[1] These recommendations have provided guidance to clinicians and researchers and have been widely cited. Since then, the results of several randomised clinical trials and cohort analyses have become available and the EULAR recommendations on imaging in LVV have been published recently.[2]

In light of these and other fundamental developments affecting key areas of management, the goal of the current project was to re-evaluate the literature in order to update the EULAR recommendations for the management of LVV.

METHODS

The recommendations were drafted according to the 2014 update of the EULAR standardised operating procedures (SOPs) for the development of EULAR-endorsed recommendations and the updated version of the Appraisal of Guidelines for Research & Evaluation (AGREE II) recommendations, where applicable (see online supplementary file 1 for a full description of methods).[3 4] The task force consisted of 20 clinical experts (including rheumatologists, internists, immunologists, a neurologist, a neuro-ophthalmologist and an epidemiologist), from 11 European countries, India and China, two fellows (AA, SM), one health professional and two patients affected by the diseases under study.

Based on results of a Delphi survey among the task force, we defined eight key research questions addressing the management and treatment of LVV. As the original systematic literature review (SLR) for the 2008 recommendations dated back 10 years ago with different methodology, it was decided to conduct two completely new SLRs without time limits, focusing on general management and treatment, respectively (table 1).

The following databases were used: MEDLINE, EMBASE and Cochrane CENTRAL. Each article was assigned a level of evidence (LoE) according to the standards of the Oxford Centre for Evidence-Based Medicine and was systematically assessed for bias.[3] The methods and results of the two SLRs are published separately.[5 6]

During a face-to-face meeting, task force members independently voted on each recommendation. Agreement on each recommendation and on the

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Table 1 Topics for the systematic literature search

SLR 1: General Management	SLR 2: Treatment
► Diagnosis: recognition, referral criteria, fast-track diagnosis, role of imaging for diagnosis, role of biopsy for diagnosis, interdisciplinary work-up, considerations for sub-types of disease such as cranial/ischaemic/large vessel, isolated aortitis, IgG4-related disease, LVV disease in other vasculitides. ► Prognostic and therapeutic implications of disease phenotypes: cranial vs extra-cranial, isolated aortitis, other forms including IgG-4 related disease, imaging, other biomarkers, comorbidities and complications, disease damage versus activity. ► Long-term follow-up of patients: clinical assessments and frequency, imaging, patient-reported outcomes, physical therapies and management of complications. ► Patient education and other aspects of patients-centred care.	► Drug therapy: dosing, length of therapy, outcome and treatment-related side effects for the following drugs: glucocorticoids, methotrexate and other non-biological immunosuppressive agents, tocilizumab and other biological agents. ► Specific treatment of organ complications: loss of vision and stroke), relapsing, refractory, glucocorticoid-dependent disease. ► Revascularisation procedures: indications for referral, management of aneurysms and/or vessel stenosis. ► Adjunctive therapies and prophylaxis: aspirin, cardiovascular and cerebrovascular disease, infections, vaccination, osteoporosis.

LVV, large vessel vasculitis; SLR, systematic literature review.

overarching principles on a scale of 0–10 (10 meaning full agreement) was given anonymously after the meeting by e-mail. A research agenda was formulated based on controversial issues and gaps in the evidence. The final manuscript was approved by the EULAR Executive Committee.

RESULTS

General aspects

The objective of the updated recommendations is to give advice on the management of LVV to rheumatologists and other health professions involved in the care of these patients. Because EULAR recommendations on imaging in LVV have been published recently,[2] the task force agreed to refer to these recommendations removing topics regarding imaging from the update of the management recommendations.

To reduce confusion currently existing in the literature we propose new consensus definitions for disease activity states in LVV (table 2), based on the concept of activity states developed for the EULAR recommendations for small vessel vasculitides (SVV).[7]

The new definitions are consensus based and do not derive from the SLR. They differ in some details from definitions used in recent clinical trials (for comparison see online supplementary file 2). By analogy to the EULAR definitions for SVV,[7] we suggest using the term 'relapse' consistently, but avoiding the term 'flare'. We propose a distinction between major and minor relapses because the prognosis and treatment of relapses in LVV depends on the presence of ischaemia and/or development or progression of vascular damage. In contrast to SVV, true refractory disease in LVV is very rare because patients usually respond well to high dose glucocorticoids (GCs). However, in the past, the term 'refractory' was sometimes used for patients with LVV and GC-dependent disease that relapsed when GCs were tapered. We propose that the activity state 'refractory' should be used to reflect the difficulty in achieving disease control despite the patient remaining on an appropriate treatment schedule (which would include tapering of the GC dose).

In 2012, IgG4-related (peri-)aortitis and isolated aortitis, either primary or secondary to infection (eg, syphilis) or other systemic diseases were recognised as separate entities by the Chapel Hill consensus conference.[8] The SLR revealed only very low evidence on management of these rare entities, which did not allow us to generate separate recommendations. Therefore, we encourage further research on these subtypes, as outlined in the research agenda below.

Overarching principles

The task force identified general principles that were deemed fundamental for the management of patients with LVV (table 3). These principles were consensus based and did not directly result from the SLR. The overarching principles and the specific recommendations are listed in table 3.

Recommendations

All patients presenting with signs and symptoms suggestive of GCA should be urgently referred to a specialist team for further multidisciplinary diagnostic work-up and management

Untreated active GCA is an emergency and carries a substantial risk of permanent visual loss and other ischaemic complications. Therefore, we recommend that all patients ≥50 years of age presenting with acute or subacute onset of signs and symptoms suggestive of GCA (table 4) and raised inflammatory

Table 2 EULAR consensus definitions for disease activity states in GCA and other types of LVV

Activity state	EULAR consensus definition
Active disease	1. The presence of typical signs or symptoms of active LVV (table 4). 2. At least one of the following: a. Current activity on imaging or biopsy. b. Ischaemic complications attributed to LVV. c. Persistently elevated inflammatory markers (after other causes have been excluded).
Flare	We do not recommend use of this term
Relapse	We recommend use of the terms major relapse or minor relapse as defined below
Major relapse	Recurrence of active disease with either of the following: a. Clinical features of ischaemia* (including jaw claudication, visual symptoms, visual loss attributable to GCA, scalp necrosis, stroke, limb claudication). b. Evidence of active aortic inflammation resulting in progressive aortic or large vessel dilatation, stenosis or dissection.
Minor relapse	Recurrence of active disease, not fulfilling the criteria for a major relapse
Refractor'y	Inability to induce remission (with evidence of reactivation of disease, as defined above in 'Active disease') despite the use of standard care therapy
Remission	Absence of all clinical signs and symptoms attributable to active LVV and normalisation of ESR and CRP; in addition, for patients with extracranial disease there should be no evidence of progressive vessel narrowing or dilatation (frequency of repeat imaging to be decided on an individual basis)
Sustained remission	1. Remission for at least 6 months. 2. Achievement of the individual target GC dose.
Glucocorticoid-free remission	Sustained remission Discontinued GC therapy (but could still be receiving other immunosuppressive therapy)

*Some symptoms listed are typical only for GCA and may require further diagnostic work-up if present in other types of LVV.
GC, glucocorticoid; GCA, giant cell arteritis; LVV, large vessel vasculitis.

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Table 3 EULAR recommendations for the management of LVV—2018 update

		LoE	SoR	FV (%)	LoA (0–10)
	Overarching principles				
A	Patients with LVV should be offered best care which must be based on a shared decision between the patient and the rheumatologist, considering efficacy, safety and costs	n.a.	n.a.	n.a.	9.7±0.7
B	Patients should have access to education focusing on the impact of LVV, it's key warning symptoms and its treatment (including treatment-related complications)	n.a.	n.a.	n.a.	9.7±0.7
C	Patients with LVV should be screened for treatment-related and cardiovascular comorbidities. We recommend prophylaxis and life-style advice to reduce cardiovascular risk and treatment-related complications	n.a.	n.a.	n.a.	9.8±0.7
	Recommendations				
1	All patients presenting with signs and symptoms suggestive of GCA should be urgently referred to a specialist team for further multidisciplinary diagnostic work-up and management	2b	C	91	9.2±2.1
2	All patients presenting with signs and symptoms suggestive of TAK should be referred to a specialist team for multidisciplinary diagnostic work-up and management	5	D	100	9.6±0.9
3	A suspected diagnosis of LVV should be confirmed by imaging (ultrasound* or MRI§ for temporal or other cranial arteries, ultrasound, CT, PET-CT or MRI for the aorta/extracranial arteries#) or histology (TAB*)	*1b §2b #3	*A §B #C	*100 §100 #100	9.5±0.9 9.3±1.2 9.6±0.8
4	High dose glucocorticoid (GC) therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active GCA& or TAK+ Once disease is controlled, we recommend tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months and after 1 year to ≤5 mg/day (for GCA) and to ≤10 mg/day (for TAK)	&4 +5 5	&C +D D	&100 +100 87	9.8±0.6 9.8±0.5 9.5±0.9
5	Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using tocilizumab**. Methotrexate may be used as an alternative§§	**1b §§1a-	**A §§A	**100 §§100	9.4±0.8 9.4±0.8
6	Non-biologic disease modifying agents should be given in combination with GC in all patients with TAK#. Tocilizumab or TNF-inhibitors can be considered in case of relapsing or refractory disease despite conventional DMARD therapy#	4	C	100	9.4±1.2
7	In case of major relapse (either with signs or symptoms of ischaemia or progressive vascular inflammation) we recommend reinstitution or dose escalation of GC therapy as recommended for new onset disease.## For minor relapses we recommend an increase in GC dose at least to the last effective dose.* Initiation or modification of adjunctive therapy should be considered particularly after recurrent disease relapses&&	##2b &&1b	##C &&A	##95 &&95	9.5±1.0 9.6±1.0
8	Antiplatelet or anticoagulant therapy should not be routinely used for treatment of LVV unless it is indicated for other reasons (eg, coronary heart disease or cerebrovascular disease etc). In special situations such as vascular ischaemic complications or high risk of cardiovascular disease, these might be considered on an individual basis	4	C	100	9.4±0.8
9	In LVV, elective endovascular interventions or reconstructive surgery should be performed in phases of stable remission. However, arterial vessel dissection or critical vascular ischaemia requires urgent referral to a vascular team	4	C	95	9.8±0.5
10	Regular follow-up and monitoring of disease activity in patients with LVV is recommended, primarily based on symptoms, clinical findings and ESR/CRP levels	3b	C	100	9.6±0.6

The LoE was determined for different parts of each recommendation (referred to with different signs such as * or §). The level of agreement was computed on a 0–10 scale.
DMARD, disease modifying anti-rheumatic drug; FV, final vote (% of expert panel members that agreed to the recommendation); LVV, large vessel vasculitis; LoA, level of agreement; LoE, level of evidence; NA, not applicable; SoR, strength of recommendation; TAB, temporal artery biopsy; TAK, Takayasu arteritis; TNF, tumour necrosis factor.

markers without explanation (eg, infection) should be referred urgently to a specialist team/experienced centre for further diagnostic work-up. This team or centre should have expertise in the disease, have rapid access to up-to-date imaging[2] and temporal artery biopsy (TAB) and should offer fast referral. Patients with new onset of visual symptoms should be seen as soon as possible by an ophthalmological team to exclude other causes of sudden visual disturbance. In case of signs of cerebral ischaemia, rapid review by a neurologist is recommended.

Results from two retrospective cohort studies have shown that immediate treatment of GCA patients and rapid referral to a specialised centre ('fast-track clinic') for diagnostic work-up, including imaging, within 24 hours after presenting with signs and symptoms of GCA can reduce the rate of permanent visual impairment compared with historical cohorts with routine non-urgent referral.[9 10] Although these studies were retrospective and therefore subject to bias, the available limited evidence supports rapid referral in order to confirm the diagnosis of GCA.[11]

Patients with both typical symptoms and increased C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR) who present with acute visual disturbance should be treated before the appointment, as delaying GC therapy when visual loss is present is the strongest risk factor for permanent blindness.[12] For patients without visual symptoms, there was no consensus among the task force members as to whether pre-emptive treatment with GCS should be started in all cases of suspected GCA in addition to fast referral to a specialised centre. In any case, pre-emptive therapy should only be given for a short period of time and should not delay early referral because the sensitivity of diagnostic tests decreases following treatment with GCs and to avoid unnecessary exposure to GCs of cases for whom the diagnosis of GCA is eventually not maintained. Although, the sensitivity of diagnostic tests decreases following treatment, imaging and biopsy may show features of GCA even weeks after GC therapy.[13–16] Therefore, diagnostic tests to confirm a suspected diagnosis of GCA should be performed in all patients irrespective of the duration of pre-emptive therapy.

All patients presenting with signs and symptoms suggestive of TAK should be referred to a specialist team for multidisciplinary diagnostic work-up and management

The majority of symptoms of TAK (table 4) are non-specific, but should prompt a thorough examination of the arterial tree. Because there is no gold standard for the diagnosis of TAK,

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Table 4 Key symptoms and clinical findings suggestive of active large vessel vasculitis

Giant cell arteritis	Takayasu arteritis
Key symptoms ► New-onset of persistent localised headache, often in the temporal area. ► Constitutional symptoms (eg, weight loss >2 kg, low-grade fever, fatigue, night sweats). ► Jaw and/or tongue claudication. ► Acute visual symptoms such as amaurosis fugax, acute visual loss, diplopia. ► Symptoms of polymyalgia rheumatica. ► Limb claudication.	Key symptoms ► New onset or worsening of limb claudication. ► Constitutional symptoms (eg, weight loss >2 kg, low-grade fever, fatigue, night sweats). ► Myalgia, arthralgia, arthritis. ► Severe abdominal pain. ► Stroke, seizures (non-hypertensive), syncope, dizziness. ► Paresis of extremities. ► Myocardial infarct, angina. ► Acute visual symptoms such as amaurosis fugax or diplopia.
Key findings on clinical examination ► Tenderness and / or thickening of the superficial temporal arteries with or without reduced pulsation. ► Scalp tenderness. ► Bruits (particularly in the axilla). ► Reduced pulses/blood pressure of the upper limbs. ► Pathological findings during ophthalmologic examination including anterior ischaemic optic neuropathy, oculomotor cranial nerve palsy/palsies, central retinal artery occlusion, branch retinal artery occlusion and/or choroidal ischaemia.	Key findings on clinical examination ► Hypertension (>140/90 mm Hg). ► New loss of pulses, pulse inequality. ► Bruits. ► Carotidynia.

we recommend referral to an experienced centre for further work-up including large-vessel imaging. Studies on fast-track referral are lacking for patients with TAK. Patients with individual presentations suggesting an increased risk of ischaemic complications need a more urgent referral.

A suspected diagnosis of LVV should be confirmed by imaging (ultrasound or MRI for temporal or other cranial arteries, ultrasound, CT, positron-emission-tomgraphy (PET)T-CT or MRI for the aorta/extracranial arteries) or histology (TAB)

Every effort should be made to confirm a suspected diagnosis of LVV. In rare cases, both imaging and biopsy are negative. If the clinical probability in such cases is high, a provisional diagnosis of GCA may be made, which needs to be confirmed or revised during follow-up.

The original recommendations advised TAB in every case of suspected GCA.[1] Since then, a large amount of good-quality data demonstrated that imaging and biopsy have similar diagnostic value if assessors are proficient in these techniques.[2 13] The recently published EULAR recommendations for the use of imaging in LVV in clinical practice contain comprehensive advice regarding when and how the different imaging modalities should best be used in different subsets of LVV.[2] Several studies have shown that neither imaging nor TAB are 100% sensitive.[2 13 17–19] Imaging of the temporal arteries by ultrasound or MRI identifies only 77% and 73% of cases, respectively, with clinical diagnosis as reference standard for GCA.[14 20 21] Thus, performing a second test can be considered if the first was negative but the clinical suspicion of GCA persists.

Ultrasound guidance appears not to improve the diagnostic yield of TAB.[22] Biopsies should be at least 1 cm in length, which corresponds to a postfixation length of at least 0.7 cm.[17] Biopsy of the contralateral artery does not add significantly to the diagnostic yield and is therefore not routinely recommended. Overall, available data do not provide convincing evidence that any individual characteristics of the biopsy findings (eg, composition or intensity of the inflammatory infiltrate) are sufficiently predictive for subsequent clinical events to allow guidance of treatment decisions or follow-up in clinical practice.[23–35]

ESR and CRP are typically elevated in GCA, and it is highly infrequent (<3%) that both are normal.[36 37] While several other serological biomarkers have been evaluated, none is sufficiently sensitive and specific for detection and assessment of disease activity or prediction of prognosis to recommend its use in clinical practice.

In patients with atypical clinical presentations not compatible with current disease definitions,[8] an alternative diagnosis or overlapping associated diseases should be considered, in the diagnostic work up, such as for example aortitis related to IgG4-related disease, LVV in anti-neutrophil-cytoplasm (ANCA)-associated vasculitis (AAV) or other vasculitides (eg, Behçet's syndrome), or LVV secondary to spondyloarthropathies, relapsing polychondritis or infections.

High dose GC therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active GCA or TAK. Once disease is controlled, we recommend tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months and after 1 year to ≤5 mg/day (for GCA) and to ≤10 mg/day (for TAK)

Induction treatment with a starting GC dose of 40–60 mg per day (all GC doses discussed in this article are prednis(ol)one equivalent) leads to remission in the majority of patients with LVV.[38–43] Although the maximum genomic effect of GCs is around 100 mg of prednisone-equivalent,[44] there is no clear evidence that starting doses of above 60 mg per day are more effective than 60 mg per day in the prevention of ischaemic events or other relevant endpoints. It should be noted that the genomic effects of glucocorticoids depend on certain patient-specific pharmacokinetic and pharmacodynamic factors. These include for example total cell number (indirectly quantified by weight), numbers of glucocorticoid receptors per cell, and glucocorticoid receptor binding affinity.[45 46] The relatively high variability of these factors explains why neither the dose-dependent efficacy of a glucocorticoid therapy can be predicted absolutely correctly, nor a weight-adapted therapy with glucocorticoids is recommended. As a consequence, and since differences between certain dosages or weight-adapted glucocorticoid dosages have not been rigourosly tested in clinical trials, the current recommendations provide dose ranges.

In patients with GCA *with* acute visual loss or amaurosis fugax, the administration of 0.25–1 g intravenous methylprednisolone for up to 3 days should be considered, because these high doses have both genomic and rapid non-genomic effects.[44 45] However, there are only low-quality retrospective clinical data supporting this recommendation.[47 48] Referral for intravenous GC therapy should not delay treatment with oral GC. The SLR revealed quality issues in both randomised controlled clinical trials (RCTs) of high dose pulse intravenous GC therapy in patients *without* visual symptoms.[40 41] In view of the limited quality of evidence, the task force recommends limiting the use of intravenous pulse GC therapy to patients with complicated GCA such as those with GCA-related visual symptoms.

We recommend tapering the GC dose, once remission has been achieved. A GC taper regimen must weigh the risk of relapse against the risk of GC-related adverse events. In GCA, relapses

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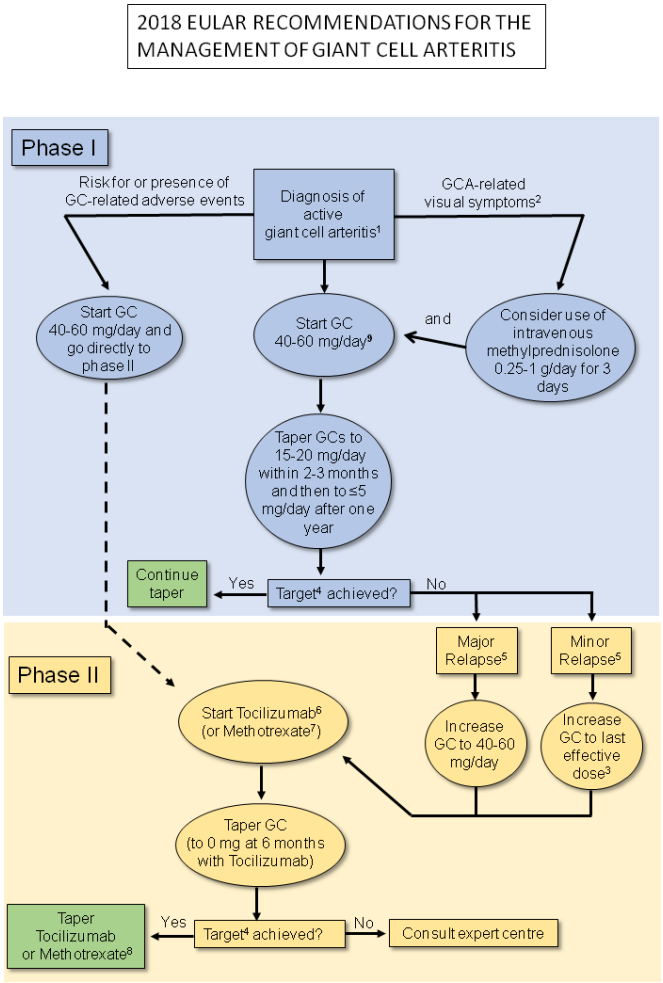
2018 EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF GIANT CELL ARTERITIS
Phase I
Risk for or presence of GC-related adverse events
Diagnosis of active giant cell arteritis[1]
GCA-related visual symptoms[2]
Start GC 40-60 mg/day and go directly to phase II
Start GC 40-60 mg/day[9]
and
Consider use of intravenous methylprednisolone 0.25-1 g/day for 3 days
Taper GCs to 15-20 mg/day within 2-3 months and then to ≤5 mg/day after one year
Continue taper
Yes
Target[4] achieved?
No
Major Relapse[5]
Minor Relapse[5]
Phase II
Start Tocilizumab[6] (or Methotrexate[7])
Increase GC to 40-60 mg/day
Increase GC to last effective dose[3]
Taper GC (to 0 mg at 6 months with Tocilizumab)
Taper Tocilizumab or Methotrexate[8]
Yes
Target[4] achieved?
No
Consult expert centre

Figure 1 The 2018 EULAR algorithm for pharmacological treatment of giant cell arteritis (GCA). GC, glucocorticoids. [1]A clinical diagnosis of GCA should be confirmed by either imaging or biopsy[2]; acute loss of vision, amaurosis fugax[3] ;or 5–15 mg/day above the last effective dose[4];the treatment target is sustained remission (absence of clinical signs and symptoms of active GCA+normal acute phase reactants) plus ability to taper GCs to the specified target without relapse[5];see table 2 for definitions[6];recommended dose is 162 mg[7]; minimum recommended dose is 15 mg [8];to be decided on an individual basis (lack of evidence)[9] ;in patients with GCA-related visual symptoms consider a starting dose of 60 mg prednisone per day after GC administration.

are common once the GC dose is tapered. Several large observational cohort studies have shown relapse rates of 34%–75% in patients with GCA treated with GC therapy.[33 49–58] The large variation of relapse risk in those studies was most likely due to different definitions for relapse (eg, symptoms *plus* CRP increase vs symptoms *or* CRP increase) and different tapering protocols. Each relapse requires a reinstitution or a dose-increase of GCs resulting in high cumulative GC exposure in a substantial proportion of patients which then leads to an increased risk of GC-related adverse events.[43 49 52 54 59–64]

A RCT of tocilizumab (TCZ) for treatment of GCA contained two placebo arms, one with a 26-week GC taper protocol and the other with a 52-week taper protocol.[38 65] Prednisone doses were identical in both arms until 20 mg/day with similar numbers of relapses in both groups; from week 15 onwards the arm with the faster dose reduction appeared to be associated with a higher relapse risk.[38] Data from an earlier open label prospective observational study comparing two different GC taper protocols also showed a rapid taper protocol to be less effective than a standard taper in maintaining remission.[42] For patients who are not eligible for GC sparing therapy, we advise against the use of these rapid taper regimens in standard clinical practice; they reflect clinical trial designs with the intention to test the GC sparing property of experimental adjunctive agents.

In summary, considering the increased relapse risk after early taper and/or reduction of the GC dose below 5 mg/day, we recommend tapering the GC dose in GCA to a target of 15–20 mg/day within 2–3 months and then to ≤5 mg/day after 1 year (figure 1). Despite the lack of data regarding the optimal length of GC therapy, the majority of panel members reported that it usually takes about 2 years or more before GCs can be stopped. In patients receiving GC-sparing therapy, faster GC taper and earlier withdrawal of GCs should be considered on an individual basis, given the lack of data. In patients treated with TCZ, the published rapid 26-week GC taper may be attempted in order to significantly reduce the cumulative dose. It is not known if even faster or conversely more prolonged GC withdrawal during TCZ therapy may lead to improved outcomes.

For TAK, there are no studies comparing different GC taper protocols. Clinical experience suggests that a starting dose of 40–60 mg per day is appropriate for the majority of patients, while patients with more localised disease may respond to lower initial GC doses of 25–30 mg per day. In a recent small RCT of TCZ in TAK, a taper of GC in the placebo group by 10% per week after week four resulted in a high relapse rate (around 80% during weeks 8–16).[66] A similar relapse rate in TAK patients treated with GC monotherapy was observed in a recent RCT of abatacept.[67] We therefore recommend that in patients who have reached a GC dose of 15–20 mg/day after 2–3 months, GC doses should subsequently be reduced more slowly as compared with GCA, targeting a dose of ≤10 mg/day after 1 year (figure 2).

Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using TCZ. Methotrexate may be used as an alternative

The original recommendations suggested adjunctive immunosuppressive therapy in all patients with LVV. However, although the risk of relapse in GCA is high, a substantial number of patients with GCA treated with GC monotherapy do not relapse and are able to taper the GC dose according to a target of ≤5 mg/day after 1 year,[49 50 52] a dose which the EULAR task force considered to be acceptably safe.[68] Therefore, we recommend limiting the use of adjunctive therapy to patients who have already developed, or have either an increased risk of developing GC-related side effects or complications, such as osteoporosis, diabetes, cardiovascular disease or glaucoma, or for relapsing patients irrespective of other risk factors. Given the high prevalence of comorbidities in the elderly population affected by GCA, the decision to use adjunctive immunosuppressive therapy in the individual patient should be balanced against potential risks for treatment-related complications, such as the increased risk of lower intestinal perforations reported in patients with rheumatoid arthritis receiving TCZ.[69]So far, no consistent factors have been identified at the time of diagnosis to predict an increased relapse risk and risk for subsequent high GC exposure in LVV.[49–55] Therefore, the identification of reliable predictive factors for relapse and prolonged GC requirement in LVV remains an important topic for future research.

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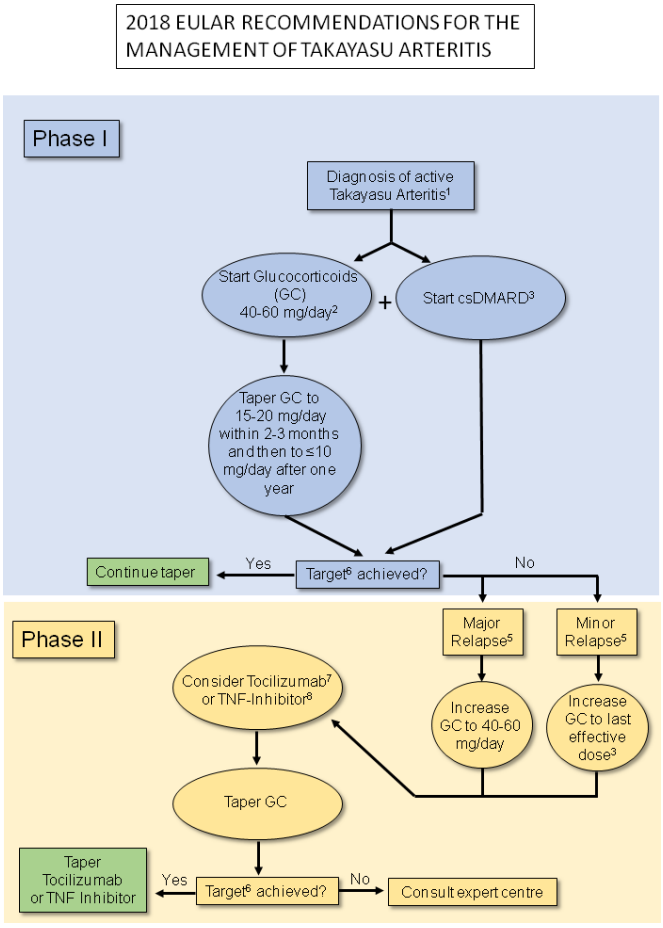

Figure 2 The 2018 EULAR algorithm for pharmacological treatment of Takayasu arteritis (TAK). csDMARD, conventional synthetic disease modifying anti-rheumatic drug; GC, glucocorticoids; TNF, tumour necrosis factor; [1]A clinical diagnosis of TAK should be confirmed by imaging[2]; in patients with more localised disease consider lower initial dose of 25–30 mg/day[3]; methotrexate or mycophenolate mofetil, leflunomide or azathioprine (when a patient does not tolerate the first choice drug switching is an option) or cyclophosphamide (only if other treatments have failed or have not been tolerated) can be used as an alternative[4]; or 5–15 mg above the last effective dose[5]; see table 2 for definitions[6]; the treatment target is sustained remission (absence of clinical signs and symptoms of active Tak associated with normal acute phase reactants) plus ability to taper GCs to the specified target without relapse[7]; tocilzumab is not formally licensed for use in TAK in the European Union (EU), the recommended dose is 162 mg one time per week s.c.[8]; Tumor necrosis factor (TNF)-inhibitors are not formally licensed for use in TAK (when a patient does not tolerate the first choice biological switching is an option).

Two high-quality randomised controlled clinical trials in patients with GCA have shown that adjunctive administration of TCZ reduces the risk of relapse and cumulative GC exposure compared with GC monotherapy.[38 70] Because TCZ suppresses CRP synthesis in the liver, the presence of a normal CRP or ESR may be falsely reassuring, although sensitivity analyses in the GiACTA trial suggest that this problem did not affect the primary outcome.[38] However, with the limited reliability of acute phase reactants for activity assessment in patients receiving TCZ, follow-up is largely symptom-based, which can make monitoring disease activity difficult. Thus, further studies on the role of imaging and other biomarkers for disease monitoring are needed. As high-quality long-term data are missing, it is not known if TCZ can reduce the risk of aneurysms or vascular stenosis. Hypothetically, the development of vascular long-term damage may occur despite TCZ therapy.[71]

Of three RCTs on the use of methotrexate (MTX) in newly diagnosed GCA,[72–74] only one[74] met its primary endpoint. As outlined in our SLR analysis in more detail, all of these trials were conducted more than 20 years ago, had differences in the study design and sample size which could have all accounted for the divergent outcomes. Importantly, the maximum weekly MTX doses of 7.5, 10 and 15 mg p.o. used in all three studies were lower than those used in clinical practice today. Despite methodological limitations of the individual studies, a high quality meta-analysis using pooled individual patient data from these trials demonstrated a reduced risk of first relapse (HR 0.65, 95% CI 0.44 to 0.98, p=0.04) and second relapse (HR 0.49, 95% CI 0.27 to 0.89, p=0.02), a higher probability of GC-free remission for ≥24 weeks (HR 2.84, 95% CI 1.52 to 5.28, p<0.001) and a lower cumulative GC dose of −842 mg at week 48 in patients treated with MTX versus controls.[75] Of note, adverse events and early withdrawals were not different between MTX and placebo groups in the metaanalysis.[75]

There are no trials comparing TCZ and MTX in GCA and the differing study designs preclude strong conclusions about the potential superiority of one agent over the other. However, compared with MTX, the effect size of TCZ in terms of relapse risk reduction and GC sparing seems larger and the meta-analysis on MTX revealed hetereogeneity of results between the individual studies. Therefore, TCZ provides a higher confidence in achieving a clinically relevant treatment effect as compared with MTX. Further studies are needed to define the optimal length of treatment, GC taper regimens, cost effectiveness and monitoring. At present, there are few and only low-quality data on long-term treatment with MTX or TCZ in GCA.[76 77] Therefore, the duration of treatment and potential dose reductions must be decided on an individual basis. As current evidence does not suggest an excessive risk of treatment-related complications of TCZ or MTX as compared with other indications,[38 75] patients should be monitored for treatment-related side effects according to existing guidelines for other diseases.[78]

Data for other adjunctive therapies are either sparse (abatacept), derived from low-quality studies (ustekinumab, azathioprine, leflunomide, cyclophosphamide, dapsone, etanercept) or negative (adalimumab, infliximab, cyclosporine).[79–90]

Non-biological disease modifying agents should be given in combination with GC in all patients with TAK. TCZ or tumour necrosis factor-inhibitors can be considered in case of relapsing or refractory disease despite conventional disease modifying anti-rheumatic drug therapy

In view of the high relapse rates of up to 70%, the development of new vascular lesions and the inability of many patients to achieve low GC doses,[91 92] we advise that early administration of a GC-sparing agent in TAK is justified and reflects current treatment practice in more recent cohorts.[93 94] However, we acknowledge that the LoE supporting this recommendations is low.

Only two RCTs, both on biological agents, have been published, neither of which met its primary endpoint for efficacy.[66 67] The evidence for a use of TCZ in TAK comes largely from one small RCT showing a statistically borderline signal (p=0.0596) towards reduced HR for the time to the first relapse and similar non-significant improvement in some secondary endpoints in the TCZ-treated patients.[66] Additional

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experience with TCZ treatment in TAK was reported from one prospective and four retrospective case series including a total of 89 patients of which the majority had refractory or relapsing disease despite treatment with GC or other agents.[95–100] Efficacy of tumour necrosis factor (TNF)-inhibitors in TAK has been reported in one prospective and several retrospective open-label uncontrolled studies/case series.[101–111] Overall, the reported reductions in disease activity in all these case series need to be interpreted with caution, because disease activity in TAK may decrease as a result of continued GC therapy over time. In contrast to the positive trends observed in GCA, the RCT of abatacept did not show any signs of efficacy in TAK.[67] Lower quality evidence from uncontrolled prospective and retrospective case series exists for the use of conventional immunosuppressive agents such as MTX, leflunomide, mycophenolate mofetil, azathioprine and cyclophosphamide in TAK.[112–117] Since TAK targets primarily women with childbearing potential and is a chronic and usually not acutely life threatening disease (unlike AAV), the use of cyclophosphamide should be limited to patients where other treatments have failed or are not tolerated. There is no high-quality evidence showing superiority of biologicals over conventional disease modifying anti-rheumatic drugs (DMARDs) in TAK.

Despite this overall low LoE, we recommend considering adjunctive treatment with conventional immunosuppressive drugs at diagnosis of TAK. A TNF-inhibitor or TCZ can be used as second line agents in case of relapsing disease. The choice of a specific immunosuppressive agent should be based on patient comorbidities or contraindications. GCs should be tapered to the lowest possible dose during treatment with immunosuppressive agents. Because good-quality data on long-term treatment of TAK are lacking, the duration of treatment must be decided on an individual basis. One study indicated that relapse risk is particularly high during the first 5 years following diagnosis.[92]

In case of major relapse (either with signs or symptoms of ischaemia or progressive vascular inflammation) we recommend reinstitution or dose escalation of GC therapy as recommended for new onset disease. For minor relapses we recommend an increase in GC dose to at least the last effective dose. Initiation or modification of adjunctive therapy should be considered particularly after recurrent disease relapses

There are no studies specifically addressing the treatment of relapse in LVV. Even larger cohort studies on relapses in GCA often lack detailed information on treatment of the relapse (GC dose, tapering, initiation of adjunctive treatment, etc).[50 51] Protocols for relapse treatment differ among RCTs and the heterogeneous study designs and adjunctive therapies do not allow for robust conclusions regarding which of the different strategies is the best.

Major relapses impose the risk of subsequent organ damage due to ischaemia and/or progressive vascular inflammation (eg, progressive large vessel stenosis) and should therefore be treated like new-onset disease with high dose GC (initial dose 40–60 mg/day) as outlined above (recommendations 3 and 4). In case of a minor relapse (eg, recurring isolated polymyalgia rheumatica (PMR) symptoms), we recommend an increase of the daily GCs dose either to the last effective dose or to 5–15 mg above this dose, the latter being common practice in many centres.

Disease relapses in LVV are most commonly but not always accompanied by an increase of ESR and CRP.[49 51 52 118] In the absence of symptoms of LVV, a rise of ESR or CRP should not automatically prompt an immediate escalation of immunosuppressive therapy. Infections should be ruled out first. If repeated measurements confirm a substantial elevation of ESR and CRP and if there is no evidence for another cause of the inflammatory response, large vessel imaging should be considered. In the presence of less specific symptoms (eg, diffuse headache) in patients with normal inflammatory markers,

Box 1 Research agenda

A. Diagnosis and classification
- Develop data-driven classification criteria for large vessel vasculitis (LVV).
- Develop data-driven diagnostic criteria for LVV.
- Develop data-driven definitions for disease activity states (remission, response, relapse) and standardisation of outcome measures used in trials for LVV.
- Develop data-driven definitions of disease subtypes of importance in giant cell arteritis (GCA).
- Identify reliable biomarkers and risk factors for relapsing disease and future vascular complications.
- Identify reliable biomarkers to assess subclinical disease activity and monitor treatment response.
- Investigate the use of the different imaging techniques for vascular activity and damage assessment and follow-up of patients with LVV, as outlined in the EULAR recommendations on imaging in LVV2.
- Investigate the role of ultrasound for guiding temporal artery biopsy.

B. Treatment
- Evaluate the effects of a mechanism-based approach to therapy (eg, IL-12/Interferon-gamma inhibition vs IL-6 inhibition).
- Identify how rapidly glucocorticoids (GCs) can be tapered in LVV.
- Identify if GC dosing based on body-weight or body surface area is superior to standard dosing.
- Investigate the effect of MTX, tocilizumab, or other adjunctive therapies and combination therapy on the development of future vascular complications in LVV.
- Investigate the optimal duration of treatment including tapering strategies and dosing (eg, higher MTX doses).
- Investigate the value of conventional (eg, leflunomide), biological and other targeted DMARDs for treatment of all forms of LVV.
- Investigate the role of anti-platelet therapy in LVV.
- Investigate predictors of response to therapy in LVV.

C. Long-term outcome and biomarkers
- Identify biomarkers which are independent of IL-6 (which could reflect response to anti-IL6 therapy).
- Identify biomarkers to predict drug toxicity.
- Identify predictors for good response, remission or relapse.
- Investigate the value of screening for aortic dilatation regarding the prevention of complications (ie, aortic dissection or aortic ruptures).
- Define and validate patient-reported outcomes in LVV.
- Investigate the role of immunosuppressive agents in other forms of LVV such as isolated aortitis or IgG4 related periaortitis.

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imaging (ultrasound, MRI or PET-CT) may be helpful.[2] However, signals of vessel wall inflammation on imaging may persist even in complete clinical remission.[16 119] At present, it is unknown if such residual activity represents true active disease or remodelling. Therefore, such imaging findings observed during follow-up have to be interpreted with caution considering the disease course of the individual patient and by comparing them to imaging findings previously obtained.[2]

As outlined in recommendation 5, we recommend adjunctive GC sparing therapy (if not already begun at disease onset) or a modification (dose escalation or switch to another agent) of an already existing GC-sparing therapy in relapsing patients in order to improve long-term disease control. So far, there are no RCTs that have specifically focused on the adjunctive treatment of relapses. However, the GiACTA trial included 132 relapsing patients and TCZ was superior to GC monotherapy in this situation.[38] All three RCTs of MTX in GCA included patients with new onset disease only. However, patients who received MTX had a 50% lower risk (p=0.02) of developing a second relapse in a meta-analysis, thus providing evidence for the efficacy of MTX after a first relapse. Other agents have either not been studied prospectively or showed no signs of efficacy in relapsing GCA.

In relapsing TAK despite treatment with GC plus a conventional immunosuppressive agent, a TNF-inhibitor or TCZ can be used as second line agent (see also recommendation 6).

Antiplatelet or anticoagulant therapy should not be routinely used for treatment of LVV unless it is indicated for other reasons (eg, coronary heart disease, cerebrovascular disease, etc). In special situations such as vascular ischaemic complications or high risk of cardiovascular disease, these might be considered on an individual basis

Patients with GCA are at an increased risk of developing cardiovascular and cerebrovascular events.[120 121] The original EULAR recommendation to use aspirin prophylactically in GCA was based on data from two retrospective studies showing that patients who received low-dose aspirin before or at the time of diagnosis of GCA may have reduced rates of vision loss or stroke, although the number of events was low in these cohorts.[122 123] However, two more recent cohort studies and a meta-analysis did not confirm a protective effect of aspirin in GCA.[124–126] Balancing the potential protective effect (which is unknown) of aspirin against its potential harm (such as bleeding),[127] we decided to change the original statement and now recommend that antiplatelet or anticoagulant therapy should not be routinely prescribed unless they are indicated for other reasons (eg, coronary heart disease, cerebrovascular disease, etc).

A significantly decreased risk of ischaemic events was reported from a single cohort of 41 TAK patients using antiplatelet therapy.[128] In view of the low LoE, a vascular team should decide on the use of anti-platelet therapy in TAK on an individual basis taking the degree of vessel stenosis and other risk factors into account.

In LVV, elective endovascular interventions or reconstructive surgery should be performed during stable remission. However, arterial vessel dissection or critical vascular ischaemia requires urgent referral to a vascular team

Interventional or surgical therapy is indicated if a vascular lesion that persists despite medical therapy is either symptomatic (such as a peripheral artery limb stenosis causing claudication) or is associated with an increased risk of future complications (such as rapid progression of an aortic aneurysm). The method of choice for vascular interventions in patients with LVV depends on the anatomic location of the vascular damage, timing (elective vs emergency) and other factors.

Undertaking surgical interventions in patients with active disease is associated with an increased risk of complications and lower patency rates.[129–132] Procedures should preferably be performed only during stable control of inflammation, except for emergency indications such as critical ischaemia, neurological complications such as stroke or aneurysm dissection. Otherwise, interventional and surgical vascular therapy follows the same principles as in patients without vasculitis.[133 134] Given the complexity of LVV, patients selected for interventional or surgical therapy should be managed in collaboration with a multidisciplinary team (the exact constituency will vary, but could include vascular radiologists, vascular surgeons, neurologists and rheumatologists).

Regular follow-up and monitoring of disease activity is recommended in patients with LVV, primarily based on symptoms, clinical findings and ESR/CRP levels

There are no data available to guide long-term follow-up of patients with GCA or TAK. In view of the high frequency of relapses and the potential harm resulting from relapse-related vessel and organ damage, routine follow-up visits could be scheduled every 1–3 months during the first year and in 3–6 months intervals afterwards. In patients with relapse-free remission, annual follow-up under shared care between rheumatologists and primary care can be considered. As late relapses can occur and the incidence of structural vascular lesions in GCA increases after 5 years from diagnosis,[49 50 135] long-term follow-up of patients with GCA that remain asymptomatic can be scheduled on an individual patient basis.

Visits should include clinical monitoring and measurement of ESR and CRP. Routine imaging for activity assessment is not recommended for patients in clinical and biochemical remission, but may be used for long-term monitoring of structural damage, particularly vessel stenosis, dilatation and/or aneurysms.[2] Methods and frequency of imaging should be decided on an individual basis.[2] LVV-specific patient-reported outcome instruments for use in clinical practice are not available,[38 136–138] and should be the subject of future research.

DISCUSSION

Since the first EULAR recommendations on the management of LVV were published, high-quality diagnostic studies and several RCTs have expanded our knowledge about these complex diseases and allowed a significant update of the original recommendations. In view of new research questions to be addressed, improvements in SOPs and methodology for the development of EULAR recommendations,[3] we undertook two completely new SLRs without time limits. Therefore, this update represents a new set of recommendations rather than a simple revision. While the majority of the original recommendations addressed LVV in general, new data allowed us to offer separate recommendations for GCA and TAK at least for some key areas of management. In GCA, disease subsets with only cranial, only extracranial or cranial plus extracranial arteritis have been described. High-quality evidence to guide differential management of these subtypes is yet lacking. Therefore,

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all recommendations on GCA management inhere refer to all subtypes of GCA.

For this update, we have made substantial alterations, including the introduction of overarching principles and new recommendations on early diagnosis, multidisciplinary management and relapse treatment.

In conclusion, we substantially revised the original recommendations for the management of LVV. Despite progress over the past 10 years, we acknowledge that many recommendations are still consensus-based. However, despite the low-LoE, the level of agreement for each recommendation was consistently high among the task force members. We encourage clinicians to implement these recommendations into their clinical practice in order to effectively manage LVV and to improve the patients' quality of care.

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EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice

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ABSTRACT

To develop evidence-based recommendations for the use of imaging modalities in primary large vessel vasculitis (LVV) including giant cell arteritis (GCA) and Takayasu arteritis (TAK). European League Against Rheumatism (EULAR) standardised operating procedures were followed. A systematic literature review was conducted to retrieve data on the role of imaging modalities including ultrasound, MRI, CT and [^{18}F]-fluorodeoxyglucose positron emission tomography (PET) in LVV. Based on evidence and expert opinion, the task force consisting of 20 physicians, healthcare professionals and patients from 10 EULAR countries developed recommendations, with consensus obtained through voting. The final level of agreement was voted anonymously. A total of 12 recommendations have been formulated. The task force recommends an early imaging test in patients with suspected LVV, with ultrasound and MRI being the first choices in GCA and TAK, respectively. CT or PET may be used alternatively. In case the diagnosis is still in question after clinical examination and imaging, additional investigations including temporal artery biopsy and/or additional imaging are required. In patients with a suspected flare, imaging might help to better assess disease activity. The frequency and choice of imaging modalities for long-term monitoring of structural damage remains an individual decision; close monitoring for aortic aneurysms should be conducted in patients at risk for this complication. All imaging should be performed by a trained specialist using appropriate operational procedures and settings. These are the first EULAR recommendations providing up-to-date guidance for the role of imaging in the diagnosis and monitoring of patients with (suspected) LVV.

INTRODUCTION

Large vessel vasculitis (LVV) is the most common form of primary vasculitis comprising giant cell arteritis (GCA) and Takayasu arteritis (TAK).[1 2] The field of GCA and LVV has undergone rapid expansion. Ultrasound-guided fast-track strategies have led to a reduction of irreversible vision loss, and the concept of imaging confirmed large vessel (LV-)GCA with or without cranial disease, has been added to the disease definition.[3–5] Based on these considerations, the importance of imaging modalities including ultrasound, MRI, CT and [^{18}F]-fluorodeoxyglucose positron emission tomography (PET) has steadily increased.[6 7] These techniques enable the assessment of cranial and extracranial arteries and the aorta and are less invasive, more sensitive and more quickly available than temporal artery biopsy (TAB) and conventional angiography, which have been the sole diagnostic standards in GCA and TAK, respectively, for decades.

In TAK, temporal arteries are usually spared, and extracranial artery biopsies are rarely feasible. Angiography visualises luminal changes caused by vasculitis such as stenosis or occlusion but cannot delineate vessel wall pathology. Besides, angiography bears the risk of allergic reactions, haematoma, iatrogenic embolisation and arterial dissection. Modern imaging methods have therefore almost replaced catheterised angiography unless it is performed for therapeutic vascular interventions.[8]

These advances have brought along significant controversy and uncertainty about when to use which imaging technique, whether imaging might be helpful during follow-up to assess disease activity and damage and whether imaging results might predict future outcomes.

The objective of this project was to provide user-friendly, evidence-based recommendations for the use of imaging modalities for diagnosis, monitoring and outcome prediction of primary LVV.

METHODS

After approval by the EULAR Executive Committee, the convenors (ChristiaD and WAS) and methodologist (SR) led a task force guided by the 2014 updated EULAR standardised operating procedures.[9] The 20 task force members consisted of rheumatologists, radiologists, nuclear medicine specialists, patient representatives, an internist, a methodologist, a healthcare professional and EMerging EUlar NETwork representatives from 10 countries. All members disclosed their potential conflicts of interest before the start of the process. Two task force meetings took place.

At the first task force meeting, the panel agreed on four key questions covering the following aspects: the role of imaging techniques (including ultrasound, MRI, CT and PET) in (1) diagnosis and (2) monitoring of inflammation and damage, (3) prediction of outcome and (4) required technical standards for imaging.

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Table 1 Oxford Centre for Evidence-Based Medicine 2011 levels of evidence for diagnostic studies (modified according to ref 13)

Level	Definition
1	Evidence from a systematic review of cross-sectional studies with consistently applied reference standard and blinding.
2	Individual cross-sectional studies with consistently applied reference standard and blinding.
3	Non-consecutive studies or studies without consistently applied reference standards.
4	Case–control studies or poor or non-independent reference standard.
5	Mechanism-based reasoning.

Level of evidence may be downgraded based on study quality, imprecision, indirectness, because of inconsistency between studies or because the absolute effect size is very small. Level may be upgraded if there is a large or very large effect size.

The systematic literature review (SLR) was conducted by two task force members (ChristinD and ChristiaD) under the guidance of the methodologist. Only prospective studies conducted in >20 patients with suspected and/or established primary LVV were included. The evidence summarised in the SLR was presented to the task force in the form of tables summarising the findings, including an assessment of the risk of bias of the studies.[10 11] The SLR is published separately[12]; however, the SLR and the present recommendations manuscript form an integral and inseparable part and should be read as such.

At the second meeting, the task force formulated the recommendations based on the evidence and expert opinion in a process of discussion and consensus, followed by final voting on the recommendations. Consensus was accepted if >75% of the members voted in favour of the recommendation at the first round, >67% at the second round and at a third round >50% was accepted. The Oxford Centre for Evidence-Based Medicine levels of evidence (LoE) derived from the SLR were added to each recommendation (table 1).[13]

Finally, each task force member anonymously indicated the level of agreement via e-mail (LoA, 0–10 numeric rating scale with 0=do not agree and 10=fully agree). The mean and SD of the LoA, as well as the percentage of task force members with an agreement ≥8 are presented.

Based on the gaps in the evidence and the issues of controversy, a research agenda was formulated. The final manuscript was reviewed and approved by all task force members and approved by the EULAR Executive Committee.

RESULTS

General aspects

These recommendations are intended to advise physicians on the use of imaging modalities (including ultrasound, MRI, CT and PET) when making a clinical diagnosis of LVV and when to apply imaging for monitoring of disease activity and damage. CT and MRI also refer to specific angiography techniques such as CT angiography (CTA) and MR angiography (MRA), and PET is commonly used in conjunction with CT or CTA.

These recommendations are not intended to cover all aspects of diagnosis and management of LVV and particularly do not discuss in full the role of TAB for GCA diagnosis.

The targeted users of these recommendations are secondary and tertiary care physicians including rheumatologists, ophthalmologists, neurologists, radiologists, nuclear medicine specialists, vascular surgeons, angiologists, geriatricians and other specialists in general (internal) medicine. The target population is patients with suspected or established primary LVV, specifically GCA or TAK. These recommendations may also inform patients participating in shared decision making, primary care physicians and healthcare providers organising care of patients with LVV.

Recommendations

A total of 12 recommendations have been formulated that are summarised in table 2 (including the LoE and LoA) and are discussed in detail below.

Recommendation 1: in patients with suspected GCA, an early imaging test is recommended to complement the clinical criteria for diagnosing GCA, assuming high expertise and prompt availability of the imaging technique. Imaging should not delay initiation of treatment.

This recommendation is general in its nature and intended to provide a framework for the subsequent specific recommendations on different imaging modalities. The choice of the individual imaging method depends on the predominant clinical symptoms and local settings as specified below. Early confirmation or exclusion of GCA by a diagnostic test is essential in order to prevent disease complications such as blindness or toxicity from unnecessary treatment.[14] The task force members recognised that many physicians still consider TAB as the gold standard test for the diagnosis of GCA. The present (and subsequent) proposition(s) should not be understood as a recommendation against performing TAB. In settings where imaging modalities are not readily available or expertise with imaging in GCA is questionable, a biopsy should still be favoured in first place. Besides, if positive histology is already available, additional imaging may not be needed for the diagnosis. In centres, however, where imaging (and TAB) is readily available and performed with high quality, the task force recommends that imaging should be preferred as the first test because of low invasiveness, ready availability of imaging results and assessment of a larger extent of potentially inflamed arteries at the same examination, thus contributing to a lower number of false negative results.

Imaging should be performed before or as early as possible after initiation of therapy, best within 1 week, because treatment with glucocorticoids rapidly reduces the sensitivity of imaging.[15–18] Treatment, however, should never be delayed in patients with a strong suspicion of GCA due to outstanding imaging or other diagnostic tests, because ischaemic complications such as blindness occur almost exclusively before initiation of therapy.[14]

The procedural risk of TAB is low; however, there is burden to patients and resource use.[19] Ultrasound in all patients with suspected GCA has been reported as cost-effective compared with biopsy plus clinical judgement alone with a net monetary benefit of £485 (€~550/US$~600) per patient.[15] Modelling of cost-effectiveness analysis considered the costs of the tests as well as the consequences of correct and incorrect diagnosis resulting in drug toxicity or vision loss that might have been prevented by one or the other test. Marking arterial segments with ultrasound to guide subsequent biopsy failed to increase the sensitivity of TAB in one randomised study[20]; however, additional research is necessary to better investigate this issue.

In patients with predominately LV-GCA, a lower sensitivity of TAB has been reported as compared with cranial GCA.[21–23] As TAB has not been conducted systematically in these studies, future studies should be conducted to investigate the diagnostic value of TAB for LV-GCA.

Recommendation 2: in patients in whom there is a high clinical suspicion of GCA and a positive imaging test, the diagnosis

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Table 2 EULAR recommendations for the use of imaging in LVV in clinical practice

Statement	LoE	LoA
1. In patients with suspected GCA, an early imaging test is recommended to complement the clinical criteria for diagnosing GCA, assuming high expertise and prompt availability of the imaging technique. Imaging should not delay initiation of treatment.	1	9.2 (2.1) 90% ≥8
2. In patients in whom there is a high clinical suspicion of GCA and a positive imaging test, the diagnosis of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely. In all other situations, additional efforts towards a diagnosis are necessary.	2	9.4 (1.0) 90% ≥8
3. Ultrasound of temporal±axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial GCA*. A non-compressible 'halo' sign is the ultrasound finding most suggestive of GCA.	1	9.7 (0.6) 100% ≧8
4. High resolution MRI† of cranial arteries‡ to investigate mural inflammation may be used as an alternative for GCA diagnosis if ultrasound is not available or inconclusive.	2	9.2 (1.1) 90% >8
5. CT† and PET† are not recommended for the assessment of inflammation of cranial arteries.	5	9.5 (1.2) 95% >8
6. Ultrasound, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of LV-GCA. Ultrasound is of limited value for assessment of aortitis.	3 (PET and CT) and 5 (MRI and ultrasound)	9.8 (0.6) 100% ≧8
7. In patients with suspected TAK, MRI to investigate mural inflammation and/or luminal changes should be used as the first imaging test to make a diagnosis of TAK, assuming high expertise and prompt availability of the technique.	3	9.1 (1.4) 90% >8
8. PET, CT and/or ultrasound may be used as alternative imaging modalities in patients with suspected TAK. Ultrasound is of limited value for assessment of the thoracic aorta.	3 (CT) and 5 (PET and ultrasound)	9.4 (0.8) 100% ≧8
9. Conventional angiography is not recommended for the diagnosis of GCA or TAK as it has been superseded by the previously mentioned imaging modalities.	5	9.8 (0.6) 100% ≥8
10. In patients with LVV (GCA or TAK) in whom a flare is suspected, imaging might be helpful to confirm or exclude it. Imaging is not routinely recommended for patients in clinical and biochemical remission.	5	9.4 (0.8) 100% ≥8
11. In patients with LVV (GCA or TAK), MRA, CTA and/or ultrasound may be used for long-term monitoring of structural damage, particularly to detect stenosis, occlusion, dilatation and/or aneurysms. The frequency of screening as well as the imaging method applied should be decided on an individual basis.	5	9.3 (1.2) 95% ≥8
12. Imaging examination should be done by a trained specialist using appropriate equipment, operational procedures and settings. The reliability of imaging, which has often been a concern, can be improved by specific training. Suggestions for technical and operational parameters are depicted in box 1.	5	9.8 (0.6) 100% ≧8

Numbers in column 'LoA' indicate the mean and SD (in parentheses) of the LoA, as well as the percentage of task force members with an agreement ≥8.
*Cranial symptoms of GCA include headache, visual symptoms, jaw claudication, swelling and/or tenderness of temporal arteries.
†CT and MRI also refers to specific angiography techniques such as CT angiography (CTA) and MR angiography (MRA), and PET is commonly combined with CT or CTA.
‡Cranial arteries: superficial temporal, occipital and facial, usually all visible in one examination in MRI.
EULAR, European League Against Rheumatism; GCA, giant cell arteritis; LoA, level of agreement; LoE, level of evidence; LV-GCA, large vessel GCA; LVV, large vessel vasculitis; PET, positron emission tomography; TAK, Takayasu arteritis.

of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely. In all other situations, additional efforts towards a diagnosis are necessary.

The performance of a diagnostic test depends on its sensitivity and specificity and on the clinical situation where it is applied, that is, on the particular pretest probability.[24] For example, a patient with 50 years of age, with chronic unspecific headache and normal inflammatory markers has a very low pretest clinical probability for the presence of GCA. Assuming a pretest probability of 5% and a positive ultrasound result (which has a 77% sensitivity and a 96% specificity),[12] the post-test probability would increase to 50% only.[24] In case of a negative test, however, the diagnosis of GCA is very unlikely with a post-test probability of 1.3%. In patients with a high clinical suspicion of GCA (>50%), for example, in case of new-onset headache, visual symptoms, jaw claudication and elevated erythrocyte sedimentation rate (ESR) and C reactive protein, a positive ultrasound would result in a post-test probability of >95%. A negative examination decreases the probability to 20%, hence, GCA is still a possible option and further investigation is necessary. In clinical practice, the pretest probability needs to be determined case by case since a clinical probability score, as it has been published for other diseases,[25] is not yet available for GCA. Estimating the pretest probability for predominately LV-GCA might be particularly challenging because symptoms of LV-GCA are often vague.

The task force clearly emphasised that in all cases, where GCA cannot be confirmed or excluded based on clinical, laboratory and imaging results, every effort towards a diagnosis should be made including additional tests such as TAB and/or additional imaging.

Recommendation 3: ultrasound of temporal±axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial GCA.[i] A non-compressible 'halo' sign is the ultrasound finding most suggestive of GCA.

Ultrasound should be the primary imaging test in patients with suspected GCA presenting predominantly with cranial symptoms because of a high LoE of good test performance, easy access, absence of radiation or other procedural risks and the relative low costs as compared with other modalities.

The 'halo' sign of temporal arteries is the most relevant ultrasound finding in GCA. Recently, it has been defined by an Outcome Measures in Rheumatology (OMERACT) working group as a 'homogenous, hypoechoic wall thickening that is well delineated towards the luminal side that is visible both in longitudinal and transverse planes, most commonly concentric in

[i]Cranial symptoms of GCA include headache, visual symptoms, jaw claudication, swelling and/or tenderness of temporal arteries.

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transverse scans'.[26] The 'halo' sign at temporal arteries revealed a pooled sensitivity of 77% and a pooled specificity of 96% as compared with the clinical diagnosis of GCA.[12] These values remained consistent in a series of sensitivity analyses.[12] The persistence of a hypoechoic swelling despite the compression of the artery lumen with the ultrasound probe (termed 'compression' sign) is a variant of the 'halo' sign revealing sensitivities of 77%–79% and a specificity of 100%.[27 28] The detection of temporal artery stenosis or occlusion did not increase the diagnostic yield over the halo sign alone.

False-positive halos might occasionally be detected in other forms of vasculitis (eg, in ANCA-associated vasculitis), in infectious diseases or in patients with (severe) arteriosclerosis.[29–31] Ultrasound results should therefore always be interpreted together with clinical and laboratory findings as stated above.

According to expert opinion, examination of axillary arteries is particularly helpful in patients with suspected GCA but negative or inconclusive temporal artery ultrasound. The SLR revealed only a slight increment in the sensitivity (2%) in one study that considered the axillary arteries as compared with the assessment of temporal arteries alone.[31] The recommendation of the task force is therefore to primarily investigate the temporal arteries. Where this examination is non-diagnostic and a clinical suspicion of GCA remains, additional vessels such as axillary or other cranial and/or extracranial arteries should be scanned.

Recommendation 4: high resolution MRI of cranial arteries[ii] to investigate mural inflammation may be used as an alternative for GCA diagnosis if ultrasound is not available or inconclusive.

High resolution MRI of superficial cranial arteries should be considered as an alternative to ultrasound. The diagnostic value of both modalities is comparable (pooled sensitivity of MRI: 73%; specificity: 88%).[12] Similarly, a retrospective direct comparison of MRI and ultrasound revealed a similar sensitivity (69% and 67%, respectively) and specificity (both 91% and 91%) of both techniques.[32]

The main limitations of MRI are restricted availability, costs and possible adverse effects of contrast agents. MRI might only be feasible if emergency referrals for GCA can be implemented. It is strongly advised not to delay GC therapy due to outstanding imaging, and MRI of cranial arteries needs to be performed immediately within the first days of GC therapy in order to avoid false-negative results.

The advantages of MRI over ultrasound are a higher standardisation of data acquisition and the possibility to investigate multiple cranial and extracranial arteries including the aorta at the same time, which might reduce the probability of missing inflammation in case of skip lesions. This requires specific technical settings with multiple coils and a long time on the MRI scanner, which is not always feasible. MRI can also assess intracranial arteries, which may be affected in GCA. Other intracranial vasculopathies such as primary cerebral angiitis, atherosclerosis or reversible cerebral vasoconstriction syndrome must be differentiated from an intracranial manifestation of GCA. In a small prospective study, the examination of intracranial arteries did not increase the diagnostic yield for GCA[33]; however, further studies are needed to investigate this issue.

Recommendation 5: CT and PET are not recommended for the assessment of inflammation of cranial arteries.

The task force does not recommend CT or PET for the assessment of cranial arteries because of lack of evidence, radiation exposure and high resource use. No studies have been conducted on these imaging modalities for the assessment of cranial arteries in GCA.[12] The use of PET is limited by the proximity of the brain; hence, superficial cranial vessels cannot be distinguished from the brain.

Recommendation 6: ultrasound, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of LV-GCA. Ultrasound is of limited value for assessment of aortitis.

This recommendation is mainly based on expert opinion. The best imaging technique for patients with suspected LV-GCA and predominantly systemic symptoms is unclear and depends on local settings and expertise. While ultrasound has advantages as outlined above, it has limited access to the thoracic aorta. Besides, the exact sensitivity and specificity of ultrasound for LV-GCA is unknown because this subgroup of patients has not been analysed separately in ultrasound studies.[31 34]

The major advantage of PET in patients with systemic symptoms is the ability to identify GCA along with other serious pathology such as infections or tumours. This may be particularly relevant in elderly patients with constitutional symptoms without specific clinical features of GCA and/or PMR. Two clinical studies reported divergent sensitivities (67%–77%) and specificities (66%–100%) for PET, which may be explained by the small sample size, the lack of independence between index test and the reference standard, use of GC as well as the circular application of different criteria for GCA.[35 36] Disadvantages of PET are high costs, lower availability and radiation exposure. Inexperienced readers may misinterpret atherosclerosis as LVV.[37] Missing information on wall-thickness and luminal changes can be overcome by combining PET with CT.

The advantages of MRI are the absence of radiation and the contemporaneous detection of structural lesions (such as vessel wall thickening and luminal stenosis/occlusion) and contrast enhancement of the arterial wall, which is presumed (but not proven) to reflect active inflammation. Specific sequences are required to image both the arterial wall and the arterial lumen as outlined in box 1. The SLR did not retrieve any study investigating the use of MRI in LV-GCA.[12]

CT may also be useful to detect structural lesions and wall inflammation and enables a higher resolution and shorter procedural time than MRI; however, this is at the cost of radiation exposure. Evidence from literature is scarce with only a single small study indicating a sensitivity of 73% and a specificity of 78% of CTA for the diagnosis of LV-GCA.[35]

Recommendation 7: in patients with suspected TAK, MRI to investigate mural inflammation and/or luminal changes should be used as the first imaging test to make a diagnosis of TAK, assuming high expertise and prompt availability of the technique.

This recommendation is almost entirely based on expert opinion and current clinical practice. A technique without radiation exposure is preferable over other modalities because of the young age of patients with TAK. Besides, MRI enables assessment of the vessel wall and luminal changes, which are both relevant for TAK. In one study, MRA yielded a sensitivity and specificity of 100% for TAK using conventional angiography as the reference standard.[38] The most important limitation of MRI is the restricted availability as compared with ultrasound or CT.

[ii]Cranial arteries: superficial temporal, occipital and facial, usually all visible in one examination in MRI.

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Box 1 Suggestions for technical and operational parameters on imaging modalities in large vessel vasculitis

Ultrasound

- High-quality, modern equipment is essential. Linear probes are recommended for supra-aortic arteries, sector or convex probes for ascending aorta and aortic arch and convex probes for abdominal aorta. Settings may slightly vary according to different equipment.
- The B-mode frequency should be ≥15 MHz for temporal arteries and 7–15 MHz for extracranial supra-aortic arteries. Image depth should be 10–20 mm for temporal arteries and 30–40 mm for extracranial supra-aortic arteries.
- The focus should be at the level of the artery. The B-mode gain should be adjusted to avoid anechoic appearance of the artery wall. The colour Doppler gain should be adjusted to avoid underfilling or overfilling of the vessel lumen.
- Colour Doppler mode is preferred over power Doppler mode. Tissue harmonic imaging may improve delineation of the intima-media complex.
- Doppler frequencies of 7–12 MHz and 4–8 MHz should be applied for the temporal and for the extracranial supra-aortic arteries, respectively. PRF should be 2–3.5 kHz and 3–4 kHz, respectively. The angle between sound waves and artery should be ≤60°.

CT

- Multislice CT scanner should be used.
- Collimation 0.6 mm, tube voltage 120 kV, tube current time product (mAs) determined by automatic dose modulation.
- Reconstruction slice thickness should be between 0.5 mm and 1.0 mm.
- Body-weight adapted injection of 60–120 mL of non-ionic iodinated contrast agent (≥ 350 mg/mL) using a power injector (≥ 4 mL/s).
- Arterial phase: bolus-tracking method (threshold of 100 HU); ECG triggering.
- Venous phase: 50 s after finishing the arterial phase acquisition.

MRI

Cranial MRI technique:

- 1.5 T, preferentially 3.0 T MRI scanner, minimum 8-channel head-coil.
- T1-weighted spin echo, gadolinium contrast-enhanced, fat-suppressed, high-resolution (inplane << 1 mm^2, for example, 195×260 µm, slice thickness 3 mm, repetition time (TR)/echo time (TE) 500/22 ms).
- T2-weighted turbo spin echo (TSE), non-contrast-enhanced imaging (TR/TE 9000/143 ms) is significantly less sensitive.
- Transversal slices angulated parallel to skull base.

Body MRI technique:

- 1.5 T, preferentially 3.0 T MRI scanner, minimum 8-channel head and neck coil and 16-channel body coil.
- MR angiography of aorta and major branches from carotid bifurcation to iliac arteries in coronal acquisition to include axillary and brachial arteries → detection of vessel lumen (stenosis, occlusion and aneurysm).
- T1-weighted, fat-suppressed, contrast-enhanced, black blood imaging (eg, navigated three-dimensional TSE, spatial resolution 1.2×1.3×2 mm^3, TR/TE 1000/35 ms) → assessment of mural inflammation.
- T2-weighted TSE imaging for oedema detection in mural inflammation is less sensitive and more prone to artefacts.

[^{18}F]-Fluorodeoxyglucose (FDG) positron emission tomography (PET)

- Hybrid PET with low-dose CT.
- Blood glucose levels: preferred <7 mmol/L (126 mg/dL), <10 mmol/L (180 mg/dL) acceptable.
- Interval between FDG infusion and image acquisition should be at least 60 min, preferably 90 min.
- Position of patient is supine, position of the arms should be arms down.
- Body parts to include: from top of head to at least midthigh, preferably to below the knees.
- Scoring FDG uptake: qualitative visual grading; if result is unclear, compare it with the liver background (grading 0–3).

Recommendation 8: PET, CT and/or ultrasound may be used as alternative imaging modalities in patients with suspected TAK. Ultrasound is of limited value for assessment of the thoracic aorta.

This recommendation is also based on expert opinion. The task force felt that PET might be particularly valuable in patients with unspecific symptoms to detect alternative causes of illness. CT (also in conjunction with PET) enables visualisation of vessel wall and luminal changes and is widely available. However, it is associated with significant radiation. Only a single small study was available for CTA yielding a sensitivity and specificity of 100% for the diagnosis of TAK using conventional angiography as the reference standard.[39] No studies were available for PET and for ultrasound. Ultrasound might be particularly valuable in patients with claudication of upper and/or lower limbs.

Recommendation 9: conventional angiography is not recommended for the diagnosis of GCA or TAK as it has been superseded by the previously mentioned imaging modalities.

Although conventional angiography has not been included formally as one of the key questions to guide the SLR, the task force felt it was necessary to make a statement. Conventional angiography has been the gold standard for several decades in the diagnosis of LVV, but it is very invasive and involves high resource use and a higher procedural risk as compared with other imaging modalities. Besides, it provides no information about wall morphology, although luminal changes are depicted with detail. The main indication for conventional angiography in LVV is currently as part of vascular interventions such as percutaneous transluminal balloon angioplasty or stenting.[40]

Recommendation 10: in patients with LVV (GCA or TAK) in whom a flare is suspected, imaging might be helpful to confirm

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Box 2 Future research agenda

- To define a gold standard for the diagnosis, particularly of large vessel giant cell arteritis (LV-GCA).
- To directly and prospectively compare the diagnostic value of ultrasound and MRI of cranial arteries for diagnosis of GCA.
- To investigate the diagnostic value of CT of cranial arteries for diagnosis of GCA.
- To compare the value of imaging for the diagnosis of GCA when performed by examiners with low versus high expertise in large vessel vasculitis (LVV) imaging.
- To investigate the additional value of imaging of axillary arteries in all patients with suspected GCA versus performing it in those without a positive imaging of temporal arteries.
- To investigate the value of standardised assessment of different vascular beds by imaging for the diagnosis of GCA.
- To investigate the role of MRI in the diagnosis of GCA in patients with a negative ultrasound.
- To investigate the possible relevance of the assessment of intracranial arteries for the diagnosis and prognosis of GCA.
- To investigate the role of ultrasound, MRI, positron emission tomography (PET) and CT in the diagnosis of LVV with predominantly systemic symptoms.
- To investigate the role of ultrasound, MRI, PET and CT in the diagnosis of Takayasu arteritis.
- To develop tools for the assessment of disease activity in LVV and to agree on definitions of remission and relapse (to better investigate the role of imaging for monitoring of LVV).
- To investigate the additional value of the different imaging modalities in the assessment of disease activity during follow-up over clinical and laboratory assessment alone.
- To investigate the value of imaging (eg, assessment of the extent of vascular involvement) as well as individual vasculitis signs (eg, 'halo' sign, contrast enhancement as compared with wall thickening) as a prognostic factor for LVV outcomes.
- To further study the possibility of differentiating persistent mural inflammation from vascular remodelling (eg, persistent fluorodeoxyglucose uptake in patients in clinical remission).
- To investigate the number of patients needed to screen with imaging methods for identifying cases with aortic complications.
- To define standardised, well-validated scoring methodologies for all imaging modalities and to develop composite scores for imaging-based monitoring of patients with LVV. To compare different imaging modalities for monitoring of aortic complications.
- To study whether therapy should be modified based on imaging results alone.
- To compare therapy modification based on traditional clinical evaluation versus evaluation that includes results of additional imaging.
- To study the value of novel technical developments for diagnosis and monitoring of LVV such as contrast-enhanced ultrasound or PET with ligands specifically targeting immune cells.

or exclude it. Imaging is not routinely recommended for patients in clinical and biochemical remission.

This recommendation is based on expert opinion. In certain situations, for example when clinical and laboratory parameters are inconclusive, imaging may determine the decision whether to change treatment. The primary choice between different imaging modalities depends again on the clinical situation, local availability and expertise. In individual patients, imaging methods might also be complementary, given that the information provided is different (such as local glucose consumption/metabolism by PET or perfusion by contrast-enhanced imaging).

In patients with a clear-cut clinical flare, as well as in patients in clinical and biochemical remission, the role of additional imaging to determine disease activity is currently unknown.

In one PET study, scans were performed in all newly diagnosed patients with GCA at baseline and during follow-up.[41] While PET scores significantly dropped from baseline to 3 months, there was no further reduction at 6 months. Up to two-thirds of patients in full clinical remission still revealed a positive PET at both follow-up visits, and PET scores did not significantly differ at times of remission and relapse. Whether ongoing tracer uptake in patients in full clinical remission is caused by low-grade inflammation or remodelling and whether these findings have any impact on future vascular outcomes are issues that have to be clarified by future studies.

Ultrasound studies in GCA reported the disappearance of the ' halo' sign in temporal arteries in the majority of patients after 2–4 weeks of GC therapy.[16 17 34 42–48] In extracranial arteries, residual changes often remained visible for several months. The examination of these vessels might be of potential value for monitoring purposes; however, none of these studies addressed whether ultrasound was helpful for the assessment of relapse.

In summary, the limited literature is mainly descriptive and does not add further insights into the additional value of imaging compared with only clinical definition of flare. Further research is urgently needed to address this issue.

Recommendation 11: in patients with LVV (GCA or TAK), MRA, CTA and/or ultrasound may be used for long-term monitoring of structural damage, particularly to detect stenosis, occlusion, dilatation and/or aneurysms. The frequency of screening as well as the imaging method applied should be decided on an individual basis.

The task force suggests, based on expert opinion, that regular screening for structural damage might be performed in GCA and TAK patients with signs or symptoms of stenosis/occlusion or aneurysms, as well as in those with recurrent or persistent inflammation of large arteries and/or the aorta. The choice of the imaging method depends on the vessel(s) affected, local settings and expertise. Monitoring of a patient with inflammation and/or dilatation of the aorta, for example, requires MRI or CT, whereas a stenosis of the axillary/subclavian arteries could be followed up by ultrasound.

The frequency of imaging assessments for vasculitic stenoses should also be decided on an individual basis, as there is currently insufficient data to frame a recommendation.[12]

The development of aortic aneurysms has been reported in patients with GCA despite the absence of ongoing clinical activity. Aortic dilatation might occur even years after disease outset.[49] Aortic inflammation at baseline as well as male sex, hypertension and smoking history have been described as risk

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factors for aortic dilatation.[50 51] However, whether and how often imaging of the aorta should be repeated remains an uncertain decision. A chest X-ray and abdominal ultrasound every other year in patients at low risk for aortic aneurysms is current clinical practice in some countries.[52] However, there are no data demonstrating that such a strategy would have a sufficient sensitivity, specificity and cost-effectiveness.[53] This is an area that requires further robust research.

Recommendation 12: imaging examination should be done by a trained specialist using appropriate equipment, operational procedures and settings. The reliability of imaging, which has often been a concern, can be improved by specific training. Suggestions for technical and operational parameters are depicted in box 1.

The task force unanimously agreed that the standardisation of investigational procedures as well as the definition of minimal technical and training requirements is essential to produce sensitive, specific and reliable imaging results.[15 54] The development of specific training programmes as well as national and international courses for imaging in LVV (particularly for ultrasound) should have a high priority in order to facilitate implementation of these recommendations in clinical practice.

The items listed in box 1 are almost entirely based on expert consensus.

No recommendation was made on the prognostic value of imaging modalities in patients with established GCA and TAK because of the absence of evidence and experience. Based on the discussions and the areas of uncertainty, a research agenda has been proposed, which is depicted in box 2.

DISCUSSION

These are the first EULAR recommendations providing up-to-date guidance for the role of imaging in the diagnosis and monitoring of patients with (suspected) LVV, recognising recent progress in the field. Imaging enables rapid diagnosis of LVV with low burden to patients and should therefore be used as the first diagnostic test provided it is readily available and performed with high quality. To implement the recommendations in clinical practice, training programmes for imaging are required. These principles are reflected in both the recommendations and the research agenda, acknowledging also the gaps in evidence that include direct comparisons of different imaging modalities, the diagnostic value of imaging for predominantly LV-GCA and TAK, as well as the specific value of imaging for monitoring and outcome prediction. Some of the recommendations were mainly based on clinical experience and consensus. Good quality studies are now required to answer the numerous questions raised in the research agenda, so that future recommendations can be upgraded and based on more solid evidence. The present recommendations nevertheless represent a step forward in the approach to patients with (suspected) LVV, and we believe that their implementation will improve patient care.

Previous EULAR recommendations for the management of LVV, already from 2009, recognised the possible value of MRI and PET for the diagnosis and assessment of TAK similar to the present prepositions, whereas for GCA, TAB was previously considered as the only reliable diagnostic test.[55] The present article is not intended to discredit the role of biopsy as clearly explained in the recommendations; nevertheless, the task force felt that TAB may be dispensable in cases where GCA is confirmed or excluded based on clinical, laboratory and imaging results.

In summary, we developed 12 recommendations on the use of imaging for the diagnosis and monitoring of LVV. These recommendations are supported by evidence along with expert consensus. Unresolved issues and areas of further study have been depicted in the research agenda. We expect that much progress continue to take place in the area of imaging in LVV, and we will carefully follow developments in the field, assuming that an amendment of these recommendations may be needed within a few years.

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2018 update of the EULAR recommendations for the management of Behçet's syndrome

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ABSTRACT

Several new treatment modalities with different mechanisms of action have been studied in patients with Behçet's syndrome (BS). The aim of the current effort was to update the recommendations in the light of these new data under the auspices of the European League Against Rheumatism (EULAR) Standing Committee for Clinical Affairs. A task force was formed that included BS experts from different specialties including internal medicine, rheumatology, ophthalmology, dermatology, neurology, gastroenterology, oral health medicine and vascular surgery, along with a methodologist, a health professional, two patients and two fellows in charge of the systematic literature search. Research questions were determined using a Delphi approach. EULAR standardised operating procedures was used as the framework. Results of the systematic literature review were presented to the task force during a meeting. The former recommendations were modified or new recommendations were formed after thorough discussions followed by voting. The recommendations on the medical management of mucocutaneous, joint, eye, vascular, neurological and gastrointestinal involvement of BS were modified; five overarching principles and a new recommendation about the surgical management of vascular involvement were added. These updated, evidence-based recommendations are intended to help physicians caring for patients with BS. They also attempt to highlight the shortcomings of the available clinical research with the aim of proposing an agenda for further research priorities.

INTRODUCTION

Behçet's syndrome (BS) is a systemic variable vessel vasculitis that involves the skin, mucosa, joints, eyes, arteries, veins, nervous system and the gastrointestinal system. Physicians from several different disciplines are involved in the care of patients with BS. The disease shows geographic differences in its clinical features. Thus a multicentre collaboration of experts from different specialties and from different parts of the world is necessary for the optimisation of the recommendations for managing BS.

The first European League Against Rheumatism (EULAR) Recommendations for the management of Behçet's disease that were published in 2008 has gained a lot of interest and helped physicians from different disciplines in the management of patients with BS.[1] At that time a total of nine recommendations were formed after a literature review, a Delphi exercise and two expert consensus meetings by a task force that included rheumatologists, ophthalmologists, dermatologists, a neurologist and a patient. In five of the nine recommendations, the strength of the recommendation was 'D', indicating that it was based only on expert opinion for the whole or at least a part of the recommendation.

The task force felt that there was a need for updating these recommendations as there had been several related new publications and data with new agents were available. Especially the experience with the use of biological agents in BS has substantially increased during the recent years. There is also more evidence to guide us in the management of gastrointestinal involvement and about other issues such as the use of anticoagulants in BS patients with vascular involvement. One of the shortcomings of the previous recommendations was that it lacked guidance regarding the surgical and interventional treatment options for vascular involvement.

The objective of the current project was to update and improve the EULAR Recommendations for the management of BS in the light of the new studies, in addition to identifying the hitherto uncovered areas for future research. The target population for these recommendations includes all physicians and surgeons who are involved in the treatment of BS.

METHODS

The standard operating procedures for developing EULAR-endorsed recommendations was followed and when applicable the Appraisal of Guidelines, Research and Evaluation instrument was used.[2] A task force was formed including 20 BS experts from seven European countries and Korea, 1 healthcare professional (a nurse), 2 patients with BS, 2 fellows responsible for the systematic literature review who are EMEUNET members and 1 senior methodologist. The experts were from various specialties that are involved in the management of patients with BS including internal medicine, rheumatology, ophthalmology, dermatology, neurology, gastroenterology, oral health medicine and vascular surgery.

An initial Delphi was conducted among the task force members to identify the questions and problem areas which were not covered by

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the previous recommendations and areas that need updating. A total of 52 clinical questions were decided on with input from both physician and patient members of the task force. The questions were amalgamated and formulated into Population, Intervention, Comparison and Outcome questions for the systematic review.[3] A protocol was prepared for the systematic review according to the recommendations given in Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols and registered in International Prospective Register of Systematic Reviews before starting the systematic literature search (registration number CRD42015027033). The systematic literature search was conducted by two fellows independently and disagreements were resolved by the convenor. Systematic reviews for mucocutaneous and joint involvement and for major organ involvement including eye, vascular, nervous system and gastrointestinal system involvement are prepared in detail for publication separately (Ozguler *et al*. Management of Major Organ Involvement of Behçet's Disease: Systematic Literature Review for the Update of the EULAR Recommendations for the Management of Behçet's Syndrome, submitted for publication; Pietro *et al*. Management of Skin, Mucosa and Joint Involvement of Behçet's Syndrome: A Systematic Literature Review for Update of the EULAR Recommendations for the Management of Behçet's Syndrome, submitted for publication). These systematic reviews and the recommendations manuscript form an integral and inseparable sum and should be read as such.

MEDLINE (from 1950), EMBASE (from 1980), The Cochrane Library, including the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessments, International Pharmaceutical Abstracts Database and the http://www.ClinicalTrials.gov website were searched using the predefined keywords and keyword combinations. Any randomised controlled trial (RCT), controlled clinical trial whether open label or not comparing an active intervention (alone or in combination) in patients with BS with any other comparator (drug or placebo) were included. If controlled trials were not available for answering a specific research question, uncontrolled evidence from preferably prospective cohort studies or case series was considered. Studies including patients meeting any of the criteria sets for BS or with a given diagnosis of BS as described by the authors were considered eligible. Authors and/or sponsors were contacted when additional data were required.

Results of the systematic reviews for mucocutaneous and joint involvement and for major organ involvement including eye, vascular, nervous system and gastrointestinal system involvement were presented to the task force during a one-and-a-half-day meeting. Following these presentations, thorough discussions led to the formation of draft recommendations. At the end of the meeting, these draft recommendations were discussed again and modified accordingly. Each recommendation was designated with a strength of recommendation from A to D, where A indicates that this is based on category I evidence (data from meta-analysis of RCTs or from at least one RCT), whereas D corresponds to category IV evidence.[2]

This 'Oxford system' was used for designating the level of evidence and strength of recommendation as advised by the standard operating procedures for developing EULAR-endorsed recommendations.[2] Consensus was reached explicitly via voting with the prespecified decision to include only the statements that obtain agreement by at least 70% of the experts. Additionally, the level of agreement from 0 to 10 for each recommendation was determined by a closed vote.

RESULTS

The systematic search of the literature databases yielded 3927 articles. After reviewing the title and abstracts, 395 were selected for full-text evaluation and 11 additional articles were identified through hand search. Finally, 192 studies on the management of mucocutaneous, joint, eye, vascular, nervous system and gastrointestinal system involvement of BS were included (figure 1). The detailed methods and results of the systematic reviews for mucocutaneous and joint involvement and for major organ involvement are submitted separately. Based on the results of these systematic reviews and experts' opinions, 5 overarching principles and 10 recommendations (table 1) were formed.

Overarching principles

- BS is a condition that typically runs a relapsing and remitting course, and the goal of treatment is to promptly suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage.
- A multidisciplinary approach is necessary for optimal care.
- Treatment should be individualised according to age, gender, type and severity of organ involvement and patients' preferences.
- Ocular, vascular, neurological and gastrointestinal involvement may be associated with a poor prognosis.
- Disease manifestations may ameliorate over time in many patients.

The relapsing and remitting nature of BS and the differences in natural course of different types of organ and system involvement, as well as differences in the disease course between men and women, mandate that the treatment should be individualised accordingly. In patients with BS, skin, mucosa and joint involvement can cause impairment of quality of life but do not cause permanent damage whereas untreated eye, vascular, nervous system and gastrointestinal system involvement can cause serious damage and even death. When there is only skin, mucosa and joint involvement, treatment can be tailored according to the patient's need and how much the symptoms impact on their quality of life compared with the risks associated with adverse effects of any medication used. When chronic oral and genital ulceration caused scarring, vigorous treatment is required to prevent oropharyngeal narrowing, and obliterative and deforming genital scarring. On the other hand, when the patient has organ involvement, it is important to rapidly suppress the inflammation and prevent relapses in order to prevent loss of function. Immunosuppressives are usually necessary to accomplish this. The more severe disease course among men with an early age of disease onset prompts more aggressive treatment and increased caution during follow-up in such patients.[4] As the disease manifestations usually abate over time, treatment may be tapered and even stopped during the course of the disease.[5]

Recommendation 1: mucocutaneous involvement

Topical measures such as steroids should be used for the treatment of oral and genital ulcers. Colchicine should be tried first for the prevention of recurrent mucocutaneous lesions especially when the dominant lesion is erythema nodosum or genital ulcer. (Level of evidence: IB; strength of recommendation: A)

Papulopustular or acne-like lesions are treated with topical or systemic measures as used in acne vulgaris. (Level of evidence: IV; strength of recommendation: D)

Leg ulcers in BS might be caused by venous stasis or obliterative vasculitis. Treatment should be planned with the help of

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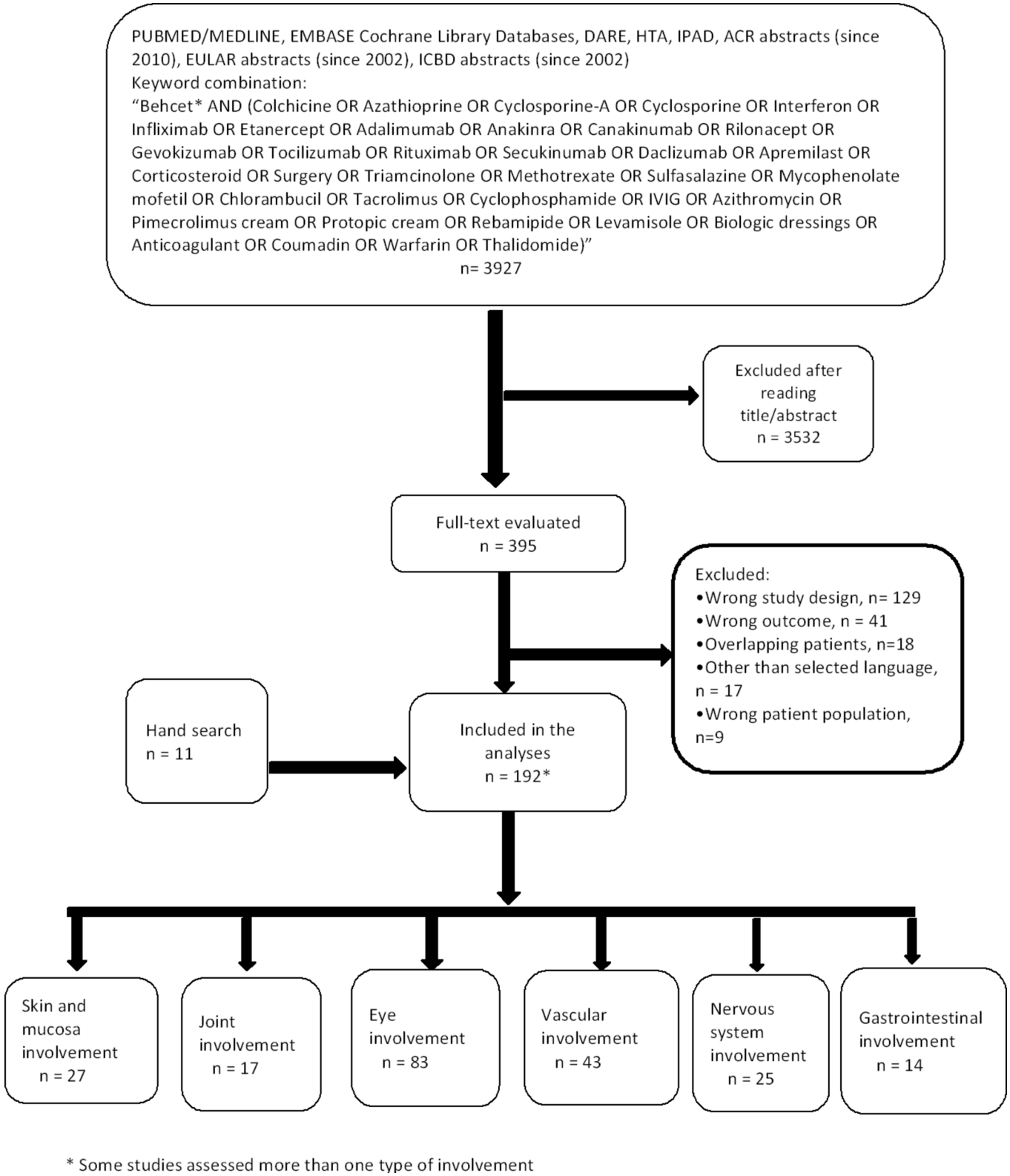
PUBMED/MEDLINE, EMBASE Cochrane Library Databases, DARE, HTA, IPAD, ACR abstracts (since 2010), EULAR abstracts (since 2002), ICBD abstracts (since 2002)
Keyword combination:
"Behcet* AND (Colchicine OR Azathioprine OR Cyclosporine-A OR Cyclosporine OR Interferon OR Infliximab OR Etanercept OR Adalimumab OR Anakinra OR Canakinumab OR Rilonacept OR Gevokizumab OR Tocilizumab OR Rituximab OR Secukinumab OR Daclizumab OR Apremilast OR Corticosteroid OR Surgery OR Triamcinolone OR Methotrexate OR Sulfasalazine OR Mycophenolate mofetil OR Chlorambucil OR Tacrolimus OR Cyclophosphamide OR IVIG OR Azithromycin OR Pimecrolimus cream OR Protopic cream OR Rebamipide OR Levamisole OR Biologic dressings OR Anticoagulant OR Coumadin OR Warfarin OR Thalidomide)"
n= 3927
Excluded after reading title/abstract n = 3532
Full-text evaluated n = 395
Excluded:
•Wrong study design, n= 129
•Wrong outcome, n = 41
•Overlapping patients, n=18
•Other than selected language, n = 17
•Wrong patient population, n=9
Hand search n = 11
Included in the analyses n = 192*
Skin and mucosa involvement n = 27
Joint involvement n = 17
Eye involvement n = 83
Vascular involvement n = 43
Nervous system involvement n = 25
Gastrointestinal involvement n = 14
* Some studies assessed more than one type of involvement

Figure 1 Flow chart of the study selection process. ACR, American College of Rheumatology; DARE, Database of Abstracts of Reviews of Effects; EULAR, European League Against Rheumatism; HTA, Health Technology Assessments; ICBD, The International Criteria for Behçet's Disease; IPAD, International Pharmaceutical Abstracts Database.

a dermatologist and vascular surgeon. (Level of evidence: IV; strength of recommendation: D)

Drugs such as azathioprine, thalidomide, interferon-alpha, tumour necrosis factor-alpha inhibitors or apremilast should be considered in selected cases. (Level of evidence: IB; strength of recommendation: A)

Several RCTs explored the efficacy of different immunomodulatory and immunosuppressive agents for mucocutaneous lesions. Colchicine was shown to be effective for genital ulcers and nodular lesions especially in women, but there was some controversy regarding its efficacy in oral ulcers.[6–8] The efficacy of colchicine and immunosuppressives for papulopustular or

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Table 1 Updated European League Against Rheumatism recommendations for the management of Behçet's syndrome, with levels of evidence, grade of recommendations, voting rates and level of agreement

	Overarching principles and recommendations	Level of evidence*	Strength of recommendation †	Level of agreement
Overarching principles	► BS is a condition that typically runs a relapsing and remitting course and the goal of treatment is to promptly suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage. ► A multidisciplinary approach is necessary for optimal care. ► Treatment should be individualised according to age, gender, type and severity of organ involvement and patient's preferences. ► Ocular, vascular, neurological and gastrointestinal involvement may be associated with a poor prognosis. ► Disease manifestations may ameliorate over time in many patients.	NA	NA	9.5±0.7
1. Mucocutaneous involvement	Topical measures such as steroids should be used for the treatment of oral and genital ulcers. Colchicine should be tried first for the prevention of recurrent mucocutaneous lesions especially when the dominant lesion is erythema nodosum or genital ulcer (IB). Papulopustular or acne-like lesions are treated with topical or systemic measures as used in acne vulgaris (IV).	IB/IV	A/D	9.4±0.8
	Leg ulcers in BS might be caused by venous stasis or obliterative vasculitis. Treatment should be planned with the help of a dermatologist and vascular surgeon.	IV	D	
	Drugs such as azathioprine, thalidomide, interferon-alpha, TNF-alpha inhibitors or apremilast should be considered in selected cases.	IB	A	
2. Eye involvement	Management of uveitis of BS requires close collaboration with ophthalmologists with the ultimate aim of inducing and maintaining remission. Any patient with BS and inflammatory eye disease affecting the posterior segment should be on a treatment regime such as azathioprine (IB), cyclosporine-A (IB), interferon-alpha (IIA) or monoclonal anti-TNF antibodies (IIA). Systemic glucocorticoids should be used only in combination with azathioprine or other systemic immunosuppressives (IIA).	IB/IIA	A/B	9.5±0.6
	Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, infliximab or interferon-alpha. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment.	IIA	B	9.4±0.7
3. Isolated anterior uveitis	Systemic immunosuppressives could be considered for those with poor prognostic factors such as young age, male sex and early disease onset.	IV	D	9.0±0.8
4.Acute deep vein thrombosis	For the management of acute deep vein thrombosis in BS, glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide or cyclosporine-A are recommended.	III	C	9.3±0.8
5. Refractory venous thrombosis	Monoclonal anti-TNF antibodies could be considered in refractory patients. Anticoagulants may be added, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled out.	III	C	8.7±0.8
6. Arterial involvement	For the management of pulmonary artery aneurysms, high-dose glucocorticoids and cyclophosphamide are recommended. Monoclonal anti-TNF antibodies should be considered in refractory cases. For patients who have or who are at high risk of major bleeding, embolisation should be preferred to open surgery.	III	C	9.2±0.9
	For both aortic and peripheral artery aneurysms, medical treatment with cyclophosphamide and corticosteroids is necessary before intervention to repair. Surgery or stenting should not be delayed if the patient is symptomatic.	III	C	9.0±1.0
7. Gastrointestinal involvement	Gastrointestinal involvement of BS should be confirmed by endoscopy and/or imaging. NSAID ulcers, inflammatory bowel disease and infections such as tuberculosis should be ruled out.	III	C	9.2±0.9
8. Refractory/severe gastrointestinal involvement	Urgent surgical consultation is necessary in cases of perforation, major bleeding and obstruction. Glucocorticoids should be considered during acute exacerbations together with disease-modifying agents such as 5-ASA or azathioprine. For severe and/or refractory patients, monoclonal anti-TNF antibodies and/or thalidomide should be considered.	III	C	8.8±0.9
9. Nervous system involvement	Acute attacks of parenchymal involvement should be treated with high-dose glucocorticoids followed by slow tapering, together with immunosuppressives such as azathioprine. Cyclosporine should be avoided. Monoclonal anti-TNF antibodies should be considered in severe disease as first-line or in refractory patients.	III	C	9.1±1.2
	The first episode of cerebral venous thrombosis should be treated with high-dose glucocorticoids followed by tapering. Anticoagulants may be added for a short duration. Screening is needed for vascular disease at an extracranial site.	III	C	9.0±0.8

Continued

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Table 1 Continued

	Overarching principles and recommendations	Level of evidence*	Strength of recommendation †	Level of agreement
10. Joint involvement	Colchicine should be the initial treatment in BS patients with acute arthritis. Acute monoarticular disease can be treated with intra-articular glucocorticoids. Azathioprine, interferon-alpha or TNF-alpha inhibitors should be considered in recurrent and chronic cases.	IB	A	9.0±1.0

*Level of evidence indicates evidence from: IA, meta-analysis of RCTs; IB, at least one RCT; IIA, at least one controlled study without randomisation; IIB, at least one type of quasi-experimental study; III, descriptive studies, such as comparative studies, correlation studies or case–control studies; IV, expert committee reports or opinions and/or clinical experience of respected authorities.
†Strength of recommendation is based on evidence: A, category I evidence; B, category II evidence or extrapolated recommendations from category I evidence; C, category III evidence or extrapolated recommendation from category I or II evidence; D, category IV evidence or extrapolated recommendation from category II or III evidence.
5-ASA, 5-aminosalicylic acid; BS, Behçet's syndrome; NA, not applicable; NSAID, non-steroidal anti-inflammatory drug; RCT, randomised controlled trial; TNF-alpha , tumour necrosis factor-alpha.

acne-like lesions seems to be limited. Mild forms of papulopustular or acne-like lesions are treated first by topical measures as used in acne vulgaris. However, chronic recurrent lesions or severe forms mimicking acne conglobata or acne cystica require systemic measures such as retinoids, sometimes together with surgical and physical therapy. Considering the safety and good tolerability of colchicine, the group agreed that it should be tried first in patients who have only mucocutaneous involvement. In patients who present with an acute exacerbation of mucocutaneous lesions, topical corticosteroids may help the rapid healing of these lesions. For patients whose lesions continue to recur despite colchicine, immunomodulatory or immunosuppressive drugs such as azathioprine, thalidomide, interferon-alpha, tumour necrosis factor alpha inhibitors (TNFis) or apremilast can be used.[9–13] The choice of immunomodulatory or immunosuppressive drug in such patients would depend on individual patient characteristics regarding safety, the cost and availability of these agents in each country, and patient preferences. Uncontrolled observational evidence suggests that lactobacilli lozenges may be a safe alternative.[14] Dapsone and azithromycin have also been tried with beneficial results.[15 16] Among the newer biological agents, interleukin (IL)-1 blockade with anakinra and canakinumab seems to provide a partial benefit in BS patients with mucocutaneous involvement, whereas IL-17 blockade with secukinumab was ineffective and IL-6 blockade with tocilizumab worsened mucocutaneous lesions.[17–22] A very recent manuscript published after the preparation of these recommendations suggests that ustekinumab may also be beneficial.[23] Management should be planned according to patients' preferences, depending on the burden of their mucocutaneous lesions weighed against the risk of adverse drug reactions with these agents.

The management of leg ulcers may be problematic since it is associated with venous stasis caused by deep vein thrombosis and/or obliterative vasculitis causing acute and chronic arterial ischaemia. Leg ulcers may occasionally be associated with pyoderma gangrenosum and require immunosuppressives. The systematic review showed no studies guiding the management of leg ulcers, thus this part of the recommendation was based solely on expert opinion. For each patient, treatment should be planned with a dermatologist and vascular surgeon experienced with such lesions as these may require the use of immunosuppressives, antibiotics if infection is present, debridement or occlusive measures such as the use of compression bandaging.

Recommendation 2: eye involvement

Management of uveitis of BS requires close collaboration with ophthalmologists with the ultimate aim of inducing and maintaining remission. Any patient with BS and inflammatory eye disease affecting the posterior segment should be on a treatment regime such as azathioprine (level of evidence: IB; strength of recommendation: A), cyclosporine-A (level of evidence: IB; strength of recommendation: A), interferon-alpha (level of evidence: IIA; strength of recommendation: B) or monoclonal anti-TNF antibodies (level of evidence: IIA; strength of recommendation: B). Systemic glucocorticoids should be used only in combination with azathioprine or other systemic immunosuppressives. (level of evidence: IIA; strength of recommendation: B)

Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, infliximab or interferon-alpha. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment. (Level of evidence: IIA; strength of recommendation: B)

Management of uveitis requires great caution with early recognition and evaluation of the severity of the involvement and frequent monitoring of drug response in order to prevent damage causing a permanent decrease in visual acuity and eventual blindness. Close collaboration with an expert ophthalmologist is essential.

Systemic, high-dose glucocorticoids are used for rapid suppression of inflammation during acute attacks. However, glucocorticoids should never be used alone in patients with posterior uveitis. Systemic immunosuppressives such as azathioprine, cyclosporine-A, interferon-alpha, infliximab or adalimumab should be used in such patients. RCTs have shown the efficacy of azathioprine and cyclosporine-A in preserving visual acuity and preventing relapses in patients with uveitis.[9 24–26] However, there are no RCTs to guide the management of patients who are refractory to these agents. Some experts have preferred interferon-alpha and others preferred monoclonal anti-TNF antibodies for such patients. A review of the literature for open-label, observational studies or retrospective case series with these agents hinted at certain differences such as a rapid response and improvement in visual acuity with infliximab, a sustained response with interferon-alpha as well as high remission rates with both of these agents.[27–63] The choice of treatment would depend on patient factors such as risk of infections including tuberculosis with monoclonal anti-TNF antibodies and tolerability of interferon-alpha, physician's experience with these agents and reimbursement policies of each country.

Among the monoclonal anti-TNF antibodies, although there is more accumulated experience with infliximab, adalimumab also seems to be an effective alternative.[63–67] Switching between these agents seems to be possible in patients with primary or secondary unresponsiveness or adverse events. A very recent manuscript published after the preparation of these recommendations

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suggests that any drug-free, long-term remission after withdrawal of successful anti-TNF treatment combined with azathioprine given for 2 years is feasible in a good proportion of patients with sight-threatening ocular disease.[68] After the preparation of these recommendations, adalimumab has been approved for the treatment of non-infectious intermediate, posterior and panuveitis by the European Medicines Evaluation Agency and the US Food and Drug Administration based on two RCTs. However, results for patients with BS, which comprised a small portion of the study population in these trials, were not provided.[64 69]

Whether immunosuppressives such as azathioprine or cyclosporine-A should be used together with monoclonal anti-TNF antibodies was discussed. Although there are no controlled data, some experts felt that concomitant use of azathioprine and/or cyclosporine-A with monoclonal anti-TNF antibodies may improve the outcome. A retrospective case series of patients with BS who were prescribed monoclonal anti-TNF antibodies for different types of involvement suggested that concomitant use of these agents did not provide extra benefit.[63] Care should be taken since plasma concentrations of cyclosporine-A may be reduced by co-administration with azathioprine.[70]

Other biological agents such as IL-1 and IL-17 blockers have also been tried. The IL-1 blocker gevokizumab[71] and IL-17 blocker secukinumab[20] failed to meet their primary endpoints in RCTs.

Intravitreal glucocorticoid injections can be used in patients with an acute exacerbation in one eye.[72–76] However, this should be used only as an adjunct to systemic immunosuppressive therapy.

Vitrectomy should only be used in patients with complications such as vitreous condensation, coagulated vitreous haemorrhage, tractional retinal detachment, vitreoretinal or epiretinal membranes. There is no anti-inflammatory effect of this procedure in patients with uveitis.

Recommendation 3: isolated anterior uveitis

Systemic immunosuppressives could be considered for those with poor prognostic factors such as young age, male sex and early disease onset. (Level of evidence: IV; strength of recommendation: D)

Isolated anterior uveitis in patients with BS may be treated with topical agents. However, some patients may have hypopyon uveitis, which is a severe form of anterior uveitis, and some patients with isolated anterior uveitis develop posterior uveitis over time. Although it is not easy to predict which patients are at risk, it was shown that young men with an early age at disease onset have a higher risk of more severe disease. A systemic immunosuppressive such as azathioprine may be considered in such patients with the anticipation that it may have a protective effect. However, there are no data yet that show such an effect.

Recommendation 4: acute deep vein thrombosis

For the management of acute deep vein thrombosis in BS, glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide or cyclosporine-A are recommended. (Level of evidence: III; strength of recommendation: C)

In patients with BS, deep vein thrombosis is thought to result from inflammation of the vessel wall rather than hypercoagulability. Post-thrombotic syndrome is frequent especially with recurrent episodes of deep vein thrombosis and may result in leg ulcers that are very difficult to treat. One of the most controversial issues regarding the management of BS is whether deep vein thrombosis should be treated with immunosuppressives, anticoagulants or both.[77]

We performed a meta-analysis of the three retrospective studies that reported on the efficacy of immunosuppressives and/or anticoagulants for preventing recurrences of deep vein thrombosis in patients with BS.[78–80] A pooled estimate of the relapse risk of deep vein thrombosis in patients with BS treated with immunosuppressives and anticoagulants compared with those treated with only anticoagulants favoured the use of immunosuppressives with an relative risk (RR) of 0.17 (95% CI 0.08 to 0.35). On the other hand, treatment with anticoagulants and immunosuppressives compared with immunosuppressives alone did not provide a significant benefit in preventing relapses (RR 0.75, 95% CI 0.48 to 1.17).

There were no data to mandate the preference of one immunosuppressive agent over the others. Azathioprine, cyclophosphamide or cyclosporine-A are agents that can be preferred in such patients. Cyclophosphamide may be reserved for patients with extensive thrombosis of larger veins such as vena cava due to its potential adverse events.

Recommendation 5: refractory venous thrombosis

Monoclonal anti-TNF antibodies could be considered in refractory patients. Anticoagulants may be added, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled out. (Level of evidence: III; strength of recommendation: C)

There were no data to guide the management of patients with refractory venous thrombosis. Monoclonal anti-TNF antibodies may be used since beneficial results have been obtained in BS patients with refractory arterial involvement. Interferon-alpha may be tried in selected cases.

Although our meta-analysis indicated that adding anticoagulants to immunosuppressives did not decrease the relapse risk, there is a retrospective study suggesting that not using anticoagulants may increase the risk of post-thrombotic syndrome (OR 3.8, 95% CI 1.04 to 14.1).[81] The task force felt that no recommendation against anticoagulant use can be made because of the lack of prospective controlled trial data demonstrating that anticoagulants do not decrease the relapse risk and the frequency of post-thrombotic syndrome in patients with BS.

However, great caution is required with respect to bleeding in anticoagulated patients with BS. This is especially important since arterial aneurysms are closely associated with deep vein thrombosis in BS. Patients need to be scrutinised for aneurysms when starting anticoagulants and physicians should be alert about the risk of developing aneurysms during the course of treatment since almost all BS patients with aneurysms have a history of deep vein thrombosis.[82]

Recommendation 6: arterial involvement

For the management of pulmonary artery aneurysms, high-dose glucocorticoids and cyclophosphamide are recommended. Monoclonal anti-TNF antibodies should be considered in refractory cases. For patients who have or who are at high risk of major bleeding, embolisation should be preferred to open surgery. (Level of evidence: III; strength of recommendation: C)

For both aortic and peripheral artery aneurysms, medical treatment with cyclophosphamide and corticosteroids is necessary before intervention to repair. Surgery or stenting should not be delayed if the patient is symptomatic. (Level of evidence: III; strength of recommendation: C)

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The primary management of pulmonary artery aneurysms and thrombosis is with high-dose glucocorticoids and cyclophosphamide. Cyclophosphamide may be given as monthly intravenous pulses and glucocorticoids are usually given as three successive intravenous methylprednisolone pulses followed by oral prednisolone (or prednisone) at a dose of 1 mg/kg/day.[83 84] Observational, uncontrolled evidence showed that infliximab provided benefit in some of the refractory patients.[85] Mortality rate has been high in surgically treated patients and surgery should not be undertaken except for life-threatening situations.[84 86 87] Embolisation may be necessary in patients with a high risk of major bleeding.[83 87 88]

Peripheral artery aneurysms require emergency surgery or stenting unless they are small, asymptomatic and carry a low risk of rupture. Medical treatment with high-dose corticosteroids and cyclophosphamide may be sufficient for such small aneurysms. Observational studies show that medical treatment is necessary in addition to surgery or stenting in order to decrease the risk of postoperative complications and recurrences.[88–90] Medical treatment should ideally start before an aneurysm repair is attempted.

For both pulmonary and peripheral artery aneurysms, the choice of surgical intervention between graft insertion, ligation and bypass surgery can be made according to the size and location of the aneurysm and the surgeon's experience. Synthetic grafts should be preferred since venous grafts have a higher risk of thrombosis in patients with BS.

Recommendation 7: gastrointestinal involvement

Gastrointestinal involvement of BS should be confirmed by endoscopy and/or imaging. NSAID ulcers, inflammatory bowel disease and infections such as tuberculosis should be ruled out. (Level of evidence: III; strength of recommendation: C)

One of the most challenging issues regarding gastrointestinal involvement is to diagnose it correctly since abdominal pain, diarrhoea and intestinal ulcers may commonly be related to other reasons such as non-steroidal anti-inflammatory drug ulcers and gastrointestinal infections including tuberculosis, especially among patients receiving immunosuppressives.[91] Confirming the diagnosis is essential to prevent the unnecessary use of immunosuppressives that may be especially harmful if the patient has an infection.

Recommendation 8: refractory/severe gastrointestinal involvement

Urgent surgical consultation is necessary in cases of perforation, major bleeding and obstruction. Glucocorticoids should be considered during acute exacerbations, together with disease-modifying agents such as 5-ASA or azathioprine. For severe and/or refractory patients, monoclonal anti-TNF antibodies and/or thalidomide should be considered. (Level of evidence: III; strength of recommendation: C)

The evidence available for the management of gastrointestinal involvement relies on retrospective observational data since there are no controlled trials for this relatively uncommon type of involvement.[91] The choice of the initial treatment modality depends on the severity of gastrointestinal involvement. Glucocorticoids are thought to help the rapid healing of ulcers during acute exacerbations. There is some concern about the potential of high-dose glucocorticoids to facilitate perforation in patients who already carry a high risk of perforation; however, there are no data to show this. Milder gastrointestinal involvement may be treated with 5-aminosalicylate derivatives whereas more severe cases can be treated with azathioprine.[91–93] Retrospective data showed that infliximab, adalimumab and thalidomide may be beneficial in patients with severe involvement, refractory to azathioprine.[94–99] Infliximab and thalidomide may be used concomitantly in selected cases.

A cohort study of BS patients with gastrointestinal involvement showed that almost a third of these patients required emergency surgery due to perforation, major bleeding or obstruction.[91] Timely recognition of these complications is very important since they may be fatal if left untreated. Immunosuppressives seem to decrease the risk of postoperative recurrences and complications in such patients.

Recommendation 9: nervous system involvement

Acute attacks of parenchymal involvement should be treated with high-dose glucocorticoids followed by slow tapering, together with immunosuppressives such as azathioprine. Cyclosporine-A should be avoided. Monoclonal anti-TNF antibodies should be considered in severe disease as first line or in refractory patients. (Level of evidence: III; strength of recommendation: C)

The first episode of cerebral venous thrombosis should be treated with high-dose glucocorticoids followed by tapering. Anticoagulants may be added for a short duration. Screening is needed for vascular disease at an extracranial site. (Level of evidence: III; strength of recommendation: C)

The two types of central nervous system involvement, namely parenchymal involvement and cerebral venous thrombosis, rarely occur in the same patient. Cerebral venous thrombosis usually manifests as an extension of vascular involvement in BS. This obviates the need of screening for early and occult vascular lesions in patients diagnosed with cerebral venous thrombosis. There are differences in the management of these two types of nervous system involvement, and the recommendations for both are supported by only uncontrolled observational studies.

For the treatment of parenchymal involvement, high-dose glucocorticoids should be started together with an immunosuppressive such as azathioprine. A typical glucocorticoid regimen would be starting with daily pulses of intravenous methylprednisolone 1 g/day that may be continued for up to 7 days followed by oral prednisolone (or prednisone) at 1 mg/kg/day for 1 month and tapered by 5–10 mg every 10–15 days. Patients who have severe parenchymal involvement at onset, those who have persistent or relapsing disease despite corticosteroids and azathioprine and patients with chronic progressive nervous system involvement that is a more severe form of parenchymal involvement may benefit from monoclonal anti-TNF antibodies.[49 63 100–103] Limited observations with tocilizumab have also shown some benefit.[104]

The task force members agreed that an acute cerebral venous thrombosis episode should be treated with high-dose glucocorticoids to obtain a rapid remission. However, there are no data showing the benefit of adding immunosuppressives in the first episode of cerebral venous thrombosis and the group felt that this may not be necessary since relapses are not frequent in this type of involvement. Anticoagulants may be added for a short duration, especially in patients who have an additional prothrombotic condition.

A meta-analysis of observational studies with cyclosporine-A showed an increased risk of nervous system involvement in patients using this agent (RR 12.66, 95% CI 4.75 to 33.76).[105–108] Thus the task force recommended to avoid cyclosporine-A in BS patients with nervous system involvement, even if the nervous system involvement is no longer active.

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Table 2 Research agenda

Eye involvement	Head-to-head trial comparing interferon-alpha to TNFis
	Controlled trials with IL-1 and IL-6 blockers
	Controlled trials assessing the comparative efficacy and safety of different TNFis
	Determining how long TNFis or interferon-alpha should be continued after remission is obtained
	Defining remission regarding a decision to switch to a maintenance therapy or considering treatment discontinuation for eye involvement
	Controlled trials determining whether glucocorticoids reduce the efficacy of interferon-alpha
Vascular involvement	Controlled trials to assess the efficacy and safety of anticoagulation for preventing relapses of venous thrombosis, post-thrombotic syndrome and recurrent arterial occlusive events
	Observational studies to identify individual differences (saccular/diffuse fusiform/large vs small) that guide the choice of surgical intervention
	Determining the optimal dose and duration of immunosuppressives after surgical intervention for peripheral artery aneurysms
	Determining the optimal treatment of postoperative recurrent anastomotic aneurysms (extra-anastomosis bypass vs local aneurysm repair)
	Determining the optimal management of intracardiac thrombosis
Nervous system involvement	Controlled studies for determining the optimal management of initial, refractory and recurrent parenchymal nervous system involvement and cerebral venous thrombosis
	Determining the role of MRI and other laboratory tests in making treatment decisions and follow-up of patients with nervous system involvement
Gastrointestinal system involvement	Controlled studies for determining the optimal management of initial, refractory and recurrent gastrointestinal system involvement
	Determining the role, optimal dose and duration of corticosteroids in acute relapses and whether they increase the risk of perforation
	Determining whether a control colonoscopy is needed in patients with clinical remission and the optimal timing for control colonoscopy
Overall	Controlled trials to assess the benefit of concomitant immunosuppressive use with TNFis
	Controlled trials assessing the efficacy of treatment modalities for patient important outcomes such as fatigue

IL, interleukin; TNFis, tumour necrosis factor alpha inhibitors.

Recommendation 10: joint involvement

Colchicine should be the initial treatment in BS patients with acute arthritis. Acute monoarticular disease can be treated with intra-articular glucocorticoids. Azathioprine, interferon-alpha or tumour necrosis factor alpha inhibitors should be considered in recurrent and chronic cases. (Level of evidence: IB; strength of recommendation: A)

Colchicine was shown to be beneficial for preventing arthritis episodes in RCTs.[6–8] Some members of the task force favoured the use of continuous low-dose corticosteroids in patients whose arthritis is not controlled with colchicine whereas others preferred azathioprine, interferon-alpha or TNFis.[9 29 34 41 63 96 109–111] Intra-articular glucocorticoids may be helpful during an acute monoarticular attack. However, this may not be necessary in many cases since the arthritis episodes are usually self-limiting and disappear in 2–3 weeks.

DISCUSSION

EULAR Recommendations for the management of BS were updated by notably revising the 2008 Recommendations and adding five overarching principles and one recommendation regarding the surgical management of arterial aneurysms. We also changed the title of the project to 'EULAR Recommendations for the Management of Behçet's Syndrome'. Some experts felt a designation of 'syndrome' was more accurate for Behçet's, actually a constellation of symptoms. The presence of geographic differences in disease expression, symptom clusters some of which are more frequent in familial cases and differences in drug response between different types of organ involvement especially with different cytokine inhibitors support this contention.[112] There was a discussion among the authors, and the disagreeing colleagues suggested that these considerations are also true for several complex and multifactorial diseases such as systemic lupus erythematosus, systemic sclerosis or antineutrophil cytoplasmic autoantibodies-associated vasculitis, none of which is called a 'syndrome'. A separate online vote was held among the authors. In total, 10/23 members preferred 'syndrome', 7/23 preferred 'disease' and 6/23 voted 'neutral'. It was also commented that this issue needed to be further discussed among a larger group of experts.

Recommendations are especially important for conditions that require the collaboration of different specialties for management. The current recommendations aim to standardise the care of patients with BS; however, there will inevitably be differences in management across countries depending on the geographic variation of the disease, differences in healthcare systems, cultural differences leading to differences in the expectations and preferences of patients and reimbursement policies. Some examples of such differences are related to the dose and duration of glucocorticoid use, more frequent use of biologics in some centres, preference of interferon-alpha instead of TNFis, anticoagulation in patients with deep vein thrombosis and the type of surgical intervention used for arterial involvement. One of the strengths of the EULAR Recommendations for the management of BS is that the task force comprised experts from several countries and from all disciplines involved in the care of patients with BS allowing the incorporation of many perspectives regarding different aspects of the disease. Another strength was the involvement of two patients with BS who were actively involved in all stages including the selection of research questions for the systematic review. The task force tried to cover management issues in different settings and different types of patients. We anticipate that these recommendations would also be useful in parts of the world where BS is less prevalent and physicians rarely facing patients with this condition or a specific type of involvement of the condition. We also aimed to guide the

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physicians on the appropriate timing for referral to a specialist centre.

Despite the continuous accrual of research data for BS management, the main limitation of these recommendations is that they were still relying on mostly observational and uncontrolled evidence and expert opinion for the treatment of vascular, gastrointestinal and nervous system involvement; as a consequence, strong recommendations were derived at by broadening the suggested management options. There were RCTs with several agents for mucocutaneous, joint and eye involvement, but very few were head-to-head trials. In potentially controversial cases any specific therapeutic option was only suggested conditionally. Moreover, the heterogeneity in study design, outcome measures and patient selection made it difficult to compare the efficacy of different agents. There is also a lack of studies evaluating the efficacy of different treatment strategies for BS such as a 'step-up' versus a 'step-down' approach. Another limitation of these recommendations is that we did not include economic considerations which can show important differences across countries.

Finally, after completing the recommendations we listed the research questions that need to be answered in the future for improving the management of patients with BS and proposed a research agenda (table 2). In particular, further research is warranted for controversial issues such as the role of anticoagulation in patients with thrombosis and the comparative efficacy of interferon-alpha and TNFis in patients with eye involvement.

In conclusion, we revised the EULAR Recommendations for the management of BS and developed 5 overarching principles and 10 recommendations related to the different types of organ and system involvement of BS. Implementation of these recommendations into clinical practice will be an important endeavour. The dissemination of the recommendations could be facilitated by translation into different languages and presentations in national meetings of different specialties involved in the management of patients with BS.

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EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

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ABSTRACT

In this article, the 2009 European League Against Rheumatism (EULAR) recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) have been updated. The 2009 recommendations were on the management of primary small and medium vessel vasculitis. The 2015 update has been developed by an international task force representing EULAR, the European Renal Association and the European Vasculitis Society (EUVAS). The recommendations are based upon evidence from systematic literature reviews, as well as expert opinion where appropriate. The evidence presented was discussed and summarised by the experts in the course of a consensus-finding and voting process. Levels of evidence and grades of recommendations were derived and levels of agreement (strengths of recommendations) determined. In addition to the voting by the task force members, the relevance of the recommendations was assessed by an online voting survey among members of EUVAS. Fifteen recommendations were developed, covering general aspects, such as attaining remission and the need for shared decision making between clinicians and patients. More specific items relate to starting immunosuppressive therapy in combination with glucocorticoids to induce remission, followed by a period of remission maintenance; for remission induction in life-threatening or organ-threatening AAV, cyclophosphamide and rituximab are considered to have similar efficacy; plasma exchange which is recommended, where licensed, in the setting of rapidly progressive renal failure or severe diffuse pulmonary haemorrhage. These recommendations are intended for use by healthcare professionals, doctors in specialist training, medical students, pharmaceutical industries and drug regulatory organisations.

INTRODUCTION

Granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) are termed the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs).[1] GPA, MPA and EGPA have respective annual incidence rates of 2.1–14.4, 2.4–10.1 and 0.5–3.7 per million in Europe, and the prevalence of AAV is estimated at to be 46–184 per million.[2–8] The 5-year survival rates for GPA, MPA and EGPA are estimated to be 74–91%, 45–76% and 60–97%, respectively.[9]

BACKGROUND AND RATIONALE

In 2009 the European League Against Rheumatism (EULAR) published recommendations for managing primary small and medium vessel vasculitis which included the management of AAV.[10] The publication of 1691 papers in the past 5 years on primary systemic vasculitis in internal medicine, rheumatology and nephrology journals, as well as the licensing of rituximab for AAV, make this an opportune time to update the recommendations with an AAV focus. This update was made in conjunction with the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA).

This paper reassesses standard therapy, including the use of biological agents, the prognostic value of histopathology and management of long-term complications, integrating these into treatment algorithms.

METHODS

The EULAR standardised operating procedure for the elaboration, evaluation, dissemination and implementation of recommendations were followed.[11] The full details are available in the online supplementary material. The task force comprised 21 members representing EULAR and ERA-EDTA: a patient (John Mills), a nurse (Janice Mooney), a pathologist (IMB), an otorhinolaryngologist (ML), a pulmonologist (BC), an immunologist (TH), an ophthalmologist (NY), two general internists (AM, MCC), six renal physicians (MAL, MS, VT, KW, AV and DRJ) and six rheumatologists (RAW, BH, JUH, RAL, PAM and CM) with academic experience and/or clinical expertise in the field of vasculitis. MY was the Clinical Fellow.

A Delphi exercise was conducted to identify items needing update and new items. This instructed the systematic literature review (SLR) strategy. The manuscripts were formally scored using the Critical Appraisal Skills Programme checklist (http://www.casp-uk.net/). Details are available in the online supplement.

STATEMENTS

The statements in this manuscript are termed 'recommendations' as opposed to 'guidelines' or 'points to consider' because they offer guidance which needs to be tailored to meet individual requirements (table 1). They are intended for use by healthcare professionals, doctors in specialist training, medical students, pharmaceutical industries and drug regulatory organisations. An algorithm has been developed to reflect the statements (figure 1).

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Table 1 Recommendation statements

Statement	Level of evidence	Grade of recommendation
1. We recommend that patients with AAV are managed in close collaboration with, or at, centres of expertise.	3	C
2. A positive biopsy is strongly supportive of a diagnosis of vasculitis and we recommend biopsies to assist in establishing a new diagnosis and for further evaluation for patients suspected of having relapsing vasculitis.	3	C
3. For remission-induction of new-onset organ-threatening or life-threatening AAV we recommend treatment with a combination of glucocorticoids and either cyclophosphamide **OR** rituximab.	1 for GPA/MPA, 3 for EGPA	A for GPA/MPA, C for EGPA
4. For remission-induction of non-organ-threatening AAV we recommend treatment with a combination of glucocorticoids and either methotrexate or mycophenolate mofetil*.	1B	B for MTX, C for MMF
5. For a major relapse of organ-threatening or life-threatening disease in AAV we recommend treatment as per new disease with a combination of glucocorticoids and either cyclophosphamide OR rituximab.	1 for GPA/MPA, 3 for EGPA and CYC, 4 for EGPA and RTX	A for GPA/MPA, C for EGPA and CYC, C for EGPA and RTX
6. (i) Plasma exchange should be considered for patients with AAV and a serum creatine level of ≥500 μmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease.	1B	B
6. (ii) Plasma exchange can also be considered for the treatment of severe diffuse alveolar haemorrhage.	3	C
7. For remission-maintenance of AAV we recommend treatment with a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil*.	1B for GPA/MPA 3 for EGPA and AZA	A for GPA/MPA, C for EGPA and AZA
8. We recommend that remission-maintenance therapy for AAV be continued for at least 24 months following induction of sustained remission.	4	D
9. For patients with AAV refractory to remission-induction therapy we recommend switching from cyclophosphamide to rituximab or from rituximab to cyclophosphamide. These patients should be managed in close conjunction with, or referred to, an expert centre for further evaluation and potential enrolment in clinical trials.	3	C
10. We recommend that structured clinical assessment rather than ANCA testing should inform decisions on changes in treatment for AAV.	4	D
11. We recommend the investigation of persistent unexplained haematuria in patients with prior exposure to cyclophosphamide.	2B	C
12. Hypoimmunoglobulinaemia has been noted after treatment with rituximab. We recommend testing of serum immunoglobulin levels prior to each course of rituximab and in patients with recurrent infection.	3	C
13. We recommend periodic assessment of cardiovascular risk for patients with AAV.	2B	B
14. We recommend that patients with AAV should be given a clear verbal explanation of the nature of their disease, the treatment options, the side effects of treatment, and the short-term and long-term prognoses.	3	C
15. We recommend that following the remission-induction phase of treatment, patients with AAV be assessed for the extent and ongoing impact of comorbidities associated with their diagnosis. Patients should then be advised where they might find the necessary therapies or support for these conditions.	4	D

*The drugs are listed in order of the strength of vote (see text).
AAV, ANCA-associated vasculities; ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; RTX, rituximab.

AAV is a very variable disease group which is unpredictable and potentially life-threatening. Treatment usually involves potent immunosuppressive drugs, often with risk of significant side effects. Full drug-free remission can be achieved but relapse is common. In addition, AAV adversely affects quality of life even in patients thought to have clinical remission.[12 13] This may be an effect of the disease or its treatment. We recommend the overarching principle of shared decision making between the patient and their specialist.

Statement 1

We recommend that patients with AAV are managed in close collaboration with, or at, centres of expertise. Level of evidence 3; grade of recommendation C; strength of vote 100%.

The rarity of AAV makes it difficult to maintain expertise in their management.[2 14–16] Assessment of these patients requires expert guidance to differentiate activity from damage or infection and to consider differential diagnoses. Patients may require interventions by specialists with expertise in AAV, such as immunological monitoring, use of rituximab in patients with refractory disease, specialised radiography, assessment of eye involvement, injection of subglottic stenosis and renal transplantation.[17–24] For patients with refractory disease, the best option may be consideration of referral to centres participating in clinical trials. AAV may relapse years after remission is achieved, even in previously unaffected organ systems.[25–27] Patients may develop complications from the treatment many years after discontinuing treatment.[28 29] Long-term follow-up and rapid access to specialist services are necessary for all patients with AAV. For these reasons patients with AAV should be managed in close collaboration with, or at, centres of expertise.[30]

Statement 2

A positive biopsy is strongly supportive of a diagnosis of vasculitis and we recommend biopsies to assist in establishing a new diagnosis and for further evaluation for patients suspected of having relapsing vasculitis. Level of evidence 3; grade of recommendation C; strength of vote 81%.

A positive biopsy for AAV is helpful when considering an initial diagnosis or recurrent disease. Histopathological evidence of vasculitis, such as pauci-immune glomerulonephritis or necrotising vasculitis in any organ, remains the gold standard for diagnostic purposes. The likely diagnostic yield varies and is dependent on the organ targeted. In patients with GPA with renal involvement the diagnostic yield from renal biopsy can be as high as 91.5%.[31] Otorhinolaryngological examination in patients with GPA often reveals abnormal findings and biopsies of these areas may be positive for inflammatory changes in up to 68.4%.[32 33] A large study of 60 nasal, 27 paranasal sinus, 17 laryngeal, 5 periorbital, 5 oral, 4 middle ear, 3 mastoid, 2 external ear and 3 salivary gland

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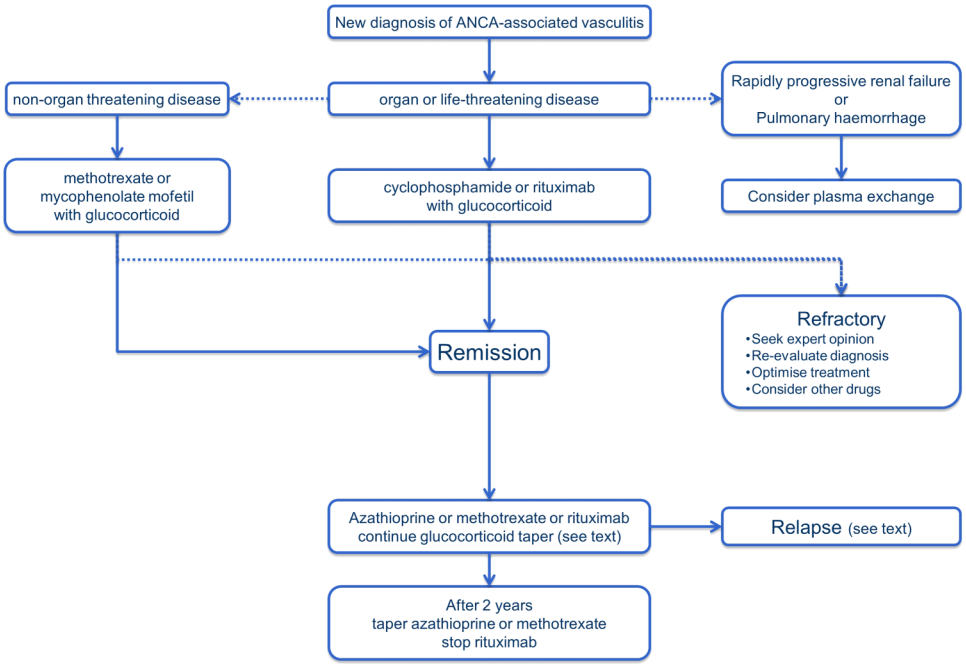

Figure 1 Algorithm to describe the management of new antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Dashed lines indicate alternative or supplementary action to consider.

biopsies revealed that they often yield non-specific chronic inflammation and the more specific findings of granulomas and vasculitis are seen less frequently than in other tissue biopsies.[34] Lung biopsies vary in their diagnostic sensitivity, with only 12% of transbronchial biopsies of alveolar tissue positive for GPA and 66.7% for EGPA in one study.[32] Open lung biopsies, although more invasive, provide a much higher diagnostic yield.[35]

Percutaneous renal biopsy should be performed using ultrasound guidance where possible and has been shown to be associated with a low risk of complications including haemorrhage.[36] The risk of bleeding following percutaneous renal biopsy is higher in patients treated with plasma exchange (PLEX).[37] Generic factors associated with an increased risk of bleeding necessitating transfusion include old age, increased systolic blood pressure and worse renal function.[38]

Existing classification systems need further validation but changes like glomerular sclerosis have obvious adverse prognostic value for patients with AAV.[39–41]

Statement 3

For remission-induction of new-onset organ-threatening or life-threatening AAV we recommend treatment with a combination of glucocorticoids and either cyclophosphamide OR rituximab.

- Cyclophosphamide
  - level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 100%.
  - level of evidence 3 for EGPA; grade of recommendation C; strength of vote 88%.
- Rituximab
  - level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 82%.
  - level of evidence 3 for EGPA; grade of recommendation C; strength of vote 59%.

Since the 1970s therapy consisting of a combination of glucocorticoids (1 mg/kg/day—maximum daily dose 80 mg) with cyclophosphamide (2 mg/kg/day—maximum 200 mg/day) has been used for remission induction in AAV.[42] Due to concerns about cumulative cyclophosphamide dosage, pulsed intravenous regimens were designed and tested, the largest study being the CYCLOPS (randomised trial of daily oral versus pulse Cyclophosphamide as therapy for ANCA-associated Systemic Vasculitis) trial.[43] This trial was designed following a meta-analysis of three studies involving 143 patients[44–46] which concluded that pulsed cyclophosphamide was more likely to achieve remission and was associated with fewer side effects than oral cyclophosphamide.[47] Long-term follow-up of the CYCLOPS cohort revealed that although the proportion of participants with at least one relapse was higher in those individuals treated with pulsed cyclophosphamide, there were no differences in survival, renal function at the end of the study or adverse events between the two arms.[48] However, pulsed regimens are favoured due to the reduced total dose of cyclophosphamide overall and reduced risk of bladder-related complications.

The grade of evidence for cyclophosphamide use in EGPA is lower than for GPA/MPA as no randomised controlled trials (RCTs) for the treatment of EGPA have been published. One study did compare cyclophosphamide doses: cyclophosphamide (0.6 mg/m^2) was used initially every 2 weeks for a month then every 4 weeks.[49] The intervention arm was given six pulses in total, while the control arm received 12 pulses. Complete remission was achieved in both groups at a similar rate (21/23 in intervention arm, 21/25 in control arm).

Antiemetic therapy should be routinely administered with intravenous cyclophosphamide. Cyclophosphamide metabolites are toxic to the urothelium and can cause haemorrhagic cystitis in the short term and malignancy in the long term.[28 29 50] If clinically appropriate, patients should be encouraged to drink plenty of fluids or given intravenous fluids on the day of the infusion to dilute the metabolites in the urine. Patients receiving pulse cyclophosphamide may also be given oral or intravenous 2-mercaptoethanesulfonate sodium (MESNA) which binds to acrolein, a toxic metabolite of cyclophosphamide, rendering it non-toxic.[26] MESNA also retards the degradation of 4-hydroxymetabolites, further reducing the toxic

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acrolein products in the urine. MESNA may also be beneficial in patients receiving continuous oral cyclophosphamide.[25 26 51]

Monitoring of patients receiving cyclophosphamide should follow standard protocols.[52] In both modalities of administration, dose changes or discontinuation of cyclophosphamide may be necessary in the event of an acute leucopenia or a gradual fall over time. In the event of a stable leucopenia, it may be possible to maintain the immunosuppression with stringent blood monitoring. We encourage prophylaxis against infection with *Pneumocystis jirovecii* with trimethoprim/sulfamethoxazole (800/160 mg on alternate days or 400/80 mg daily) in all patients being treated with cyclophosphamide, where not contraindicated.[53–55] The use of inhaled monthly pentamidine in the event of an adverse reaction or contraindication to trimethoprim/sulfamethoxazole may be useful but is not cost-effective and not routinely indicated.[53] Other alternatives include dapsone and atovaquone.

Rituximab in AAV has been tested in two RCTs (RAVE (Rituximab for the Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis) and RITUXVAS (an international, randomised, open label trial comparing a rituximab based regimen with a standard cyclophosphamide/azathioprine regimen in the treatment of active, 'generalised' ANCA associated vasculitis)).[56 57] In both studies patients initially received high-dose glucocorticoids with subsequent dose tapering. The rituximab dose in both studies was 375 mg/m^2 of body surface area, once a week for four infusions. In both trials, rituximab was non-inferior to cyclophosphamide and appeared more effective for relapsing disease in RAVE. Details of the clinical trials in this section are available in the online supplement.

The grade of evidence for the use of rituximab in patients with EGPA is lower than for GPA/MPA. A retrospective analysis of 41 patients with EGPA who received differing regimens of rituximab found that 34% achieved complete remission at 6 months and 49% at 12 months.[58]

Due to high cost, rituximab use is restricted in some countries and therefore involvement of expert centres is mandated. There may be specific instances where rituximab is preferable to cyclophosphamide, for example, in patients who wish to preserve their reproductive potential. Cyclophosphamide is associated with reduced ovarian reserve, ovarian failure and male infertility.[59–63] The long-term effects of rituximab on fertility have not been studied but no such concerns have been reported. In patients with severe disease, treatment should not be delayed but discussion of these issues should take place.

The task force considered appropriate a target of between 7.5 mg and 10 mg of prednisolone (or equivalent) after 3 months (12 weeks) of treatment. A review of the prednisolone protocol reduction regimens published for the key trials illustrated that on average a dose of 10 mg was achieved after 19 weeks, and a dose of 7.5 mg after 21 weeks (figure 2).[43 49 56 57 64–68] Therefore although a target prednisolone dose of 7.5–10mg is desirable by 3 months, in practice it may be 5 months before this is achieved.

The AAVs have protean manifestations and the spectrum of disease ranges from the indolent to the life-threatening.[69–73] Although the evidence and thus the recommendations follow current classification systems, it is not our intention to maintain this delineation in the long term and future evidence about outcomes of phenotypes may change current labels.

Statement 4

For remission-induction of non-organ-threatening AAV we recommend treatment with a combination of glucocorticoids and either methotrexate or mycophenolate mofetil.

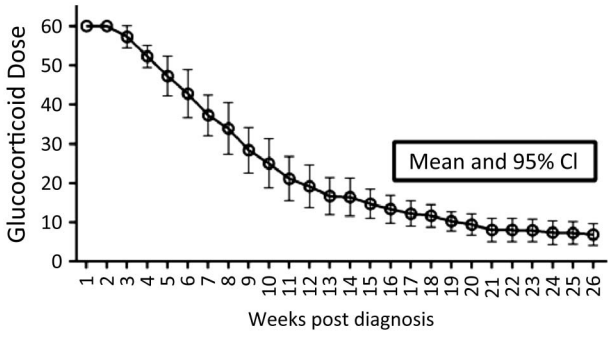

Figure 2 Protocol target prednisolone dosages in the key induction trials of antineutrophil cytoplasmic antibody associated vasculitis.

- Methotrexate
  - Level of evidence 1B; grade of recommendation B; strength of vote 77%.
- Mycophenolate mofetil
  - Level of evidence 1B; grade of recommendation C; strength of vote 65%.

The task force was keen to stress that the use of methotrexate or mycophenolate mofetil should not be used for remission induction in the following scenarios:

- Meningeal involvement
- Retro-orbital disease
- Cardiac involvement
- Mesenteric involvement
- Acute-onset mononeuritis multiplex
- Pulmonary haemorrhage of any severity

Methotrexate (20–25 mg/week, oral or parenteral) may be used as an alternative to cyclophosphamide in patients with less severe disease and in those with normal renal function.[25 65 74–81] There have been trials using either methotrexate or mycophenolate mofetil as the remission induction agent in patients with AAV.[65] Oral methotrexate 20–25 mg/week was non-inferior to oral cyclophosphamide at 6 months but long-term follow-up revealed that patients treated with methotrexate had less effective disease control as compared with those treated with cyclophosphamide.[82] Methotrexate should therefore be considered only for non-organ-threatening disease. Examples include the following in the *absence of renal involvement*

- Nasal and paranasal disease without bony involvement (erosion) or cartilage collapse or olfactory dysfunction or deafness
- Skin involvement without ulceration
- Myositis (skeletal muscle only)
- Non-cavitating pulmonary nodules/infiltrate without haemoptysis
- When cyclophosphamide or rituximab are not available or contraindicated or patient choice

The induction trials involving methotrexate are generally larger and of higher evidence grade than those using mycophenolate mofetil. To date, the two RCTs using mycophenolate mofetil have been conducted primarily in patients with MPA (of the 76 participants 75 had MPA).[83 84] MPA often affects renal function and in such situations methotrexate would not be indicated. The trials did not include patients with lung haemorrhage or central nervous system (CNS) involvement and therefore mycophenolate mofetil should not be routinely preferred in life-threatening situations.

Details of the clinical trials discussed in this statement are available in the online supplement.

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Statement 5

For a major relapse of organ-threatening or life-threatening disease in AAV we recommend treatment as per new disease with a combination of glucocorticoids and either cyclophosphamide OR rituximab.

- Rituximab
  - level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%.
  - level of evidence 4 for EGPA; grade of recommendation D; strength of vote 100%
- Cyclophosphamide
  - level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 88%.
  - level of evidence 3 for EGPA; grade of recommendation C; strength of vote 88%.

Most trials published on remission induction in AAV make no distinction between those participants treated for a new or relapsing presentation of their disease. It is for these reasons that the trial evidence for new or relapsing disease is often from the same studies. However, some studies have distinguished between those participants with new and relapsing disease and have stratified by this factor when randomising patients.

The largest RCT to investigate the use of rituximab for remission induction in AAV (RAVE) stratified participants by new or relapsing disease: those with relapsing disease treated with rituximab were more likely to be in disease remission at the 6-month and 12 month time points but not the 18 month follow-up visit.[57]

The cumulative dose of cyclophosphamide is related to toxicity and is a particular concern with prolonged oral dosing, where cumulative doses are higher.[85] For this reason the task force has favoured a greater strength of recommendation for rituximab over cyclophosphamide for relapsing disease.

The treatment of non-severe relapses in AAV with a temporary increase in the glucocorticoid dose restores disease remission in most patients but recurrent relapses within a relatively short time period remain common.[86] Given these data, alternative approaches to the treatment of non-severe relapses must be considered, especially if relapses are frequent. We therefore recommend treatment with intensification or modification of the immunosuppressive remission maintenance regimen. The details of the data are available in the online supplement.

Statement 6

Plasma exchange should be considered for patients with AAV and a serum creatine level of >500 μmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease. Level of evidence 1B; grade of recommendation B; strength of vote 77%.

Plasma exchange can also be considered for the treatment of severe diffuse alveolar haemorrhage. Level of evidence 3; grade of recommendation C; strength of vote 88%.

PLEX use is usually reserved for patients with either severe renal impairment or those with diffuse alveolar haemorrhage.[87–89] The largest trial published to date is MEPEX which recruited those individuals with either a serum creatine >500 μmol/L (5.7 mg/dL) or those requiring dialysis.[68] Long-term follow-up and analysis of this trial have also been published.[90] PLEX appeared to be of value in preventing end-stage renal disease or death at 3 months,[68] but long-term follow-up revealed no statistically significant benefit for the PLEX group.[91] A prior meta-analysis had concluded that PLEX may decrease the composite end point of end stage renal disease (ESRD) or death in patients with renal vasculitis.[92]

However most trials of PLEX did not restrict use to individuals with a serum creatine >500 μmol/L (5.7 mg/dL). One RCT with long-term follow-up tested whether PLEX may benefit individuals with a serum creatine of <500 μmol/L (5.7 mg/dL):[93] after 1 month, none of the PLEX participants required haemodialysis (HD) or had worsening renal function compared with six with declining renal function and five on HD in the reference group ($p<0.05$).[93] Despite the improvements in renal function, there were no differences in all-cause mortality between the PLEX and reference groups after 5 years of follow-up.[93] PEXIVAS (Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA) - Associated Vasculitis) is a global trial that is currently recruiting patients with moderate renal impairment (estimated glomerular filtration rate (eGFR)<50 mL/min) and aims to provide definitive answers regarding the use of PLEX in AAV.[90]

Further details about the clinical trials and the PEXIVAS protocol are available in the online supplement.

There is also potential benefit for PLEX in patients with AAV who are also anti-glomerular basement membrane (GBM) antibody positive, particularly those in whom there is linear staining of IgG on the glomerular basement membrane, and PLEX should be performed early in such patients to improve outcome.[89 94]

Statement 7

For remission maintenance of AAV we recommend treatment with a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil.

GPA/MPA

- Azathioprine
  - Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%.
- Rituximab
  - Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 59%.
- Methotrexate
  - Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 53%
- Mycophenolate mofetil
  - Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 53%

EGPA

- Azathioprine
  - Level of evidence 3 for EGPA; grade of recommendation C; strength of vote 77%.

Long-term therapy with cyclophosphamide has been used to maintain remission in patients with AAV.[25] However the toxicity of long-term cyclophosphamide makes it an unattractive option.[28 50 29] Azathioprine (2 mg/kg/day) is safer than oral cyclophosphamide but as effective at 18 months in preventing relapse.[67 95] Methotrexate (20–25 mg/kg/week) has been effectively used for maintenance therapy after induction of remission with cyclophosphamide (if the serum creatine is <130 μmol/L or 1.5 mg/dL).[96 97] Leflunomide (20–30 mg/day) may be more effective than methotrexate in remission maintenance but is associated with more adverse effects.[98] Therefore leflunomide is considered for second line treatment in cases of intolerance to azathioprine, methotrexate, mycophenolate mofetil or

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rituximab. Early cessation of therapy is associated with an increased risk of relapse.[65]

The MAINRITSAN (Efficacy Study of Two Treatments in the Remission of Vasculitis) trial compared low-dose rituximab in GPA/MPA (at a fixed 500 mg dose) to tapering dose of azathioprine for remission maintenance after induction with pulsed cyclophosphamide.[99] At month 28, major relapses had occurred: 17 in the azathioprine group and 3 in the rituximab group. Renal relapses occurred in 8/17 major relapses in the azathioprine group and 0/3 in the rituximab group.[99]

Azathioprine is preferred over mycophenolate mofetil for remission maintenance, because of the results from the IMPROVE (Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy in ANCA Associated Systemic Vasculitis) trial.[100] In both groups the remission maintenance agent was reduced at two time points (after 12 months and 18 months) and withdrawn after 42 months.[100] Relapses were noted in 42 participants treated with mycophenolate mofetil and in 30 participants in the azathioprine group ($p<0.01$).

The addition of trimethoprim/sulfamethoxazole (800/160 mg twice daily) to standard remission maintenance can reduce the risk of relapse in GPA.[101] Although trimethoprim/sulfamethoxazole has been used as the sole remission maintenance agent in half the patients of one RCT, trimethoprim/sulfamethoxazole monotherapy may not be effective for maintenance of remission.[101 102] In patients with nasal disease, treatment with topical antibiotics such as mupirocin may be considered in the presence of chronic carriage of nasal *Staphylococcus aureus*.[103]

Statement 8

We recommend that remission-maintenance therapy for AAV be continued for at least 24 months following induction of sustained remission. Level of evidence 4; grade of recommendation D; strength of vote 75% for myeloperoxidase (MPO) persistent disease, 62% for MPO negative disease, 100% for PR3 persistent disease and 92% for PR3 negative disease.

No published RCTs have directly compared duration of maintenance therapy regimens. Early cessation of therapy is associated with an increased risk of relapse.[65 104] Most of the data regarding relapse risk are derived from a combination of observational cohort data and long-term follow-up from clinical trials. There are however important differences in the make-up of the participants from these sources, with many more patients with GPA likely to be present in observational cohort studies.[105] In general, attempts at reduction of glucocorticoids should be made prior to tapering of the immunosuppressive agent. A meta-analysis of 13 studies (8 RCTs and 5 observational studies with 983 participants) examining the effect of duration of glucocorticoids on relapse rate concluded that continuing glucocorticoids is associated with fewer relapses.[106] The pooled total estimate for the proportion of patients suffering with a relapse recruited to RCTs was 36% (95% CI 25% to 47%) but only 14% for those studies which continued glucocorticoids. In patients with AAV with renal involvement, worse prognosis is associated with those who have MPO-ANCA, even after adjustment for baseline factors such as age, sex and serum creatine.[107] Furthermore, patients with MPO-ANCA have more severe tubulointerstitial inflammation and both CD3(+) T cell tubulitis and tubular atrophy are independently associated with eGFR at 12 months.[108] In addition, kidney biopsies displaying sclerosis are associated with worse outcomes in AAV.[109] However patients with PR3-ANCA and those with cardiovascular or lung involvement are more likely to relapse.[72 110] The resultant grade for the strength of recommendation of the task force reflects the lack of data for this area. It should be noted that there was a trend to increase the duration of therapy in patients who are PR3-ANCA positive and this was reflected with median of the vote for 36 months of maintenance therapy in this particular scenario.

Statement 9

For patients with AAV refractory to remission-induction therapy we recommend switching from cyclophosphamide to rituximab or from rituximab to cyclophosphamide. These patients should be managed in close conjunction with, or referred to, an expert centre for further evaluation and potential enrolment in clinical trials. Level of evidence 3; grade of recommendation C; strength of vote 71%.

Refractory disease is defined by EULAR as:[111]

- Unchanged or increased disease activity in acute AAV after 4 weeks of treatment with standard therapy in acute AAV, or
- Lack of response, defined as <50% reduction in the disease activity score (eg, Birmingham Vasculitis Activity Score (BVAS) or BVAS/wegener's granulomatosis (WG)), after 6 weeks of treatment, or
- Chronic, persistent disease defined as presence of at least one major or three minor items on the disease activity score after >12 weeks of treatment.

It is important to consider why a particular patient may have refractory disease and what is driving the conclusion that they have refractory disease. Items to consider are:

- Re-evaluate the primary diagnosis; are they truly refractory—do they have AAV?
- Has the treatment regimen been optimised, that is, have target dosages for therapy been reached?
- Is this active disease or could it be damage?
- Is the present disease due to AAV or could it be due to an infection or other comorbidity or possible malignancy?

Rituximab has proven useful in patients with refractory disease, particularly those previously treated with cyclophosphamide. Patients with refractory renal disease have the greatest chance of improvement, while those with retro-orbital disease pose a particular challenge.[58 73 112 113] Based on the results of an additional analysis of the WEGENT (Comparison of Methotrexate or Azathioprine as Maintenance Therapy for ANCA-Associated Vasculitides) trial, as a potential strategy the task force suggested a switch from pulsed to oral cyclophosphamide when rituximab is unavailable, under the guidance of an expert centre.[114]

In the follow-up of patients enrolled into the RAVE trial who failed to achieve the primary end point, treatment with blinded cross-over or according to best medical judgement by the trial physician lead to disease control in the majority.[115] Rituximab may be better than cyclophosphamide for those participants who are PR3-ANCA positive.[115]

For patients who fail to achieve remission and have persistent low activity, adjunctive therapy with intravenous immunoglobulin (IVIG) may help patients achieve remission.[116–118] Prior to therapy, serum immunoglobulin levels must be measured because patients with selective IgA deficiency may develop an anaphylactic reaction on receiving IVIG or a pre-existing hyperglobulinaemia may become aggravated leading to a hyperviscosity state.

Further details of the data discussed in this statement are available in the online supplement.

Statement 10

We recommend that structured clinical assessment rather than ANCA testing should inform decisions on changes in treatment

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for AAV. Level of evidence 4; grade of recommendation D; strength of vote 100%.

The role of ANCA testing as a means of predicting future relapse is controversial and evolving.[119–122] ANCA testing should be performed at accredited labs which take part in quality assurance testing programmes.[123 124] A negative ANCA does not rule out AAV in the appropriate clinical context of active disease.[125 126]

Some studies have shown that patients in whom the ANCA titres either persist, rise fourfold or become positive have a higher incidence of relapse, while other studies did not confirm this association.[95 121 120] We believe that these factors should not lead to a change in therapy but more frequent clinical assessment should be considered.

Multiorgan involvement is common in AAV therefore a structured clinical assessment should be conducted in all patients. This examination may be facilitated by the use of clinical tools such as BVAS and the Vasculitis Damage Index.[127–130] BVAS (V.3) was modified in 2008.[127] Other validated tools include BVAS/WG, the Disease Extent Index and the Five Factor Score.[131 132] These tools have a high degree of correlation and are reliable.[133] Training and certification in using these tools is recommended for clinicians caring for patients with AAV.

A structured examination of the patient should be carried out at each clinic visit to detect new organ involvement, which may develop at any time in the disease course.[134] Urinalysis should be performed on each patient at each visit to screen for infection, renal relapse or response, as well as bladder complications.[28 50 29] During follow-up, inflammatory markers and renal function should be measured periodically (every 1–3 months) to monitor disease status. A full blood count and liver function should be performed at similar intervals to screen for drug toxicity.[52 67] An acute fall in white cell count or a progressive leucopenia may require reduction or discontinuation of immunosuppressive drugs. Similarly, declining renal function may necessitate dose adjustment or alteration of immunosuppressive agents. Patients should have periodic assessment of their blood glucose while on glucocorticoid therapy.[10]

Statement 11

We recommend the investigation of persistent unexplained haematuria in patients with prior exposure to cyclophosphamide. Level of evidence 2B; grade of recommendation C; strength of vote 100%.

The use of cyclophosphamide is strongly associated with the risk of bladder cancer.[28 29 50] The use of MESNA as an uroprotective agent lowers the risk of haemorrhagic cystitis but there is no clear evidence that it protects against bladder cancer.[85] Transitional cell cancer can occur within months of commencement of cyclophosphamide or many years after its discontinuation.[28] Tobacco smokers are particularly susceptible and may develop the cancer at lower doses and earlier than non-smokers.[28] All patients should have periodic urinalysis for the duration of their follow-up. In the presence of haematuria confirmed on urine microscopy, an urgent urology opinion must be sought.

Statement 12

Hypoimmunoglobulinaemia has been noted after treatment with rituximab. We recommend testing of serum immunoglobulin levels prior to each course of rituximab and in patients with recurrent infection. Level of evidence 3; grade of recommendation C; strength of vote 65%.

Hypoimmunoglobulinaemia is associated with repeated use of cyclophosphamide and rituximab and is dependent on the cumulative dose of the drugs used. Cyclophosphamide treatment results in a decrease in immunoglobulin (Ig) levels and subsequent rituximab treatment in patients resulted in a further decline in Ig levels.[24] Surveying patients with AAV is warranted post cyclophosphamide and rituximab treatment for serum immunoglobulin concentrations and persisting hypoimmunoglobulinaemia.[24] In patients who develop this complication, involvement of a clinical immunologist is recommended. Not all patients who develop hypoimmunoglobulinaemia have infectious complications.[135]

Patients with AAV should be immunised against infectious disease according to local policy. It should be noted that influenza vaccination does not appear to be associated with relapse in patients with AAV.[136 137] In addition patients with GPA show an adequate immune response to influenza vaccination.[138] Vaccination against herpes zoster (follow local guidelines because this is a live vaccine which may be contraindicated in immunosuppressed patients), pneumococcus and influenza should be considered in patients with AAV. However one should take into account the patients' need for treatment of their AAV and of likely treatment choice for both induction and maintenance therapy. Live attenuated vaccines should be avoided whenever possible. We refer readers to the EULAR recommendation for vaccination in adult patients with autoimmune inflammatory rheumatic diseases.[139]

Further discussion is available in the online supplement.

Statement 13

We recommend periodic assessment of cardiovascular risk for patients with AAV. Level of evidence 2B; grade of recommendation B; strength of vote 53%.

Patients with AAV are at risk of complications, both from their disease and its treatment.[134] In AAV, renal, otolaryngological and treatment-related complications (cardiovascular disease, diabetes, osteoporosis and malignancy) and damage increase over time. Around a third of patients have ≥five items of damage at a mean of 7 years post diagnosis. At long-term follow-up, the most commonly reported items of treatment-related complications or damage were hypertension (41.5%; 95% CI 35.6% to 47.4%), osteoporosis (14.1%; 9.9% to 18.2%), malignancy (12.6%; 8.6% to 16.6%) and diabetes (10.4%; 6.7% to 14.0%). Given that hypertension and diabetes are well known cardiovascular risk factors it is perhaps unsurprising that patients with AAV are at an increased risk for cardiovascular disease. However, the risk of cardiovascular disease appears to be greater than can be explained through traditional cardiovascular risk factors alone. A comparison of 535 participants with 5-year follow-up from four European Vasculitis Society (EUVAS) trials revealed that within 5 years of diagnosis, 14% of patients with GPA or MPA will have a cardiovascular event.[140] This study also showed that independent determinants of cardiovascular outcome were: older age (OR 1.45, 95% CI 1.11 to 1.90), diastolic hypertension (OR 1.97, 95% CI 0.98 to 3.95) and PR3-ANCA (OR 0.39, 95% CI 0.20 to 0.74).[140] Annual review of traditional Framingham risk factors is appropriate.

Patients with AAV are at risk of long-term kidney damage. Guidelines exist on the management of chronic kidney disease (CKD) such as Kidney Disease: Improving Global Outcomes (KDIGO) (http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf).

Statement 14

We recommend that patients with AAV should be given a clear verbal explanation of the nature of their disease, the treatment

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options, the side effects of treatment, and the short-term and long-term prognoses. Level of evidence 3; grade of recommendation C; strength of vote 88%.

It is a generally accepted principle in medical practice that patients who are well informed and educated about their illness and understand it have better outcomes. An evaluation of patient education has taken place using an inpatient education programme in a tertiary referral centre, although this was not a RCT.[141] Patients should be encouraged to share responsibility for dealing with their illness.[141]

AAV can be a bewildering and confusing illness for patients who can be very fearful when receiving a diagnosis of such an uncommon disease. Like all rare diseases there is little common experience and understanding of vasculitis so there are no readily available sources of information. Patients with rare diseases often feel isolated and alone.[142]

The internet can now provide access to reliable and up-to-date information and advice, and to patient support groups which provide the reassurance of peer support and the ability to share knowledge and experience. The internet can also provide incorrect, unproven and even dangerous information. It is often the least articulate and least confident who are most vulnerable and need support.

AAV is characteristically a relapsing disease. Each relapse may result in further morbidity so early prediction or recognition of relapse is essential. A patient who understands and is educated about the disease is frequently better able to recognise the early signs and symptoms of relapse.

Statement 15

We recommend that following the remission-induction phase of treatment, patients with AAV be assessed for the extent and ongoing impact of comorbidities associated with their diagnosis. Patients should then be advised where they might find the necessary therapies or support for these conditions. Level of evidence 4; grade of recommendation D; strength of vote 100%.

AAV is a systemic disease with the potential to affect almost any organ.[143] Patients may be left with permanent damage to kidneys, lungs and respiratory tract, heart, peripheral and central nervous system, total or partial loss of sight or hearing.[144 145] Patients may lose digits or limbs or be left with facial disfigurement (like a saddle-nose) or severe skin scarring.[27] Severe fatigue, muscle weakness and chronic pain are frequent direct consequences of AAV.[146 147] Side effects of treatment can be serious, even life-threatening.[148]

The consequences of AAV may have a serious impact on education, employment prospects and job retention.[149] Personal and social relationships may be seriously disrupted, sometimes resulting in the total breakdown of family bonds. These factors may contribute to depression as a secondary consequence of AAV.[150 151]

AAV is a controllable but currently incurable lifelong illness. Treating clinicians need to be aware that AAV often has long-term lifestyle consequences. A 'holistic' approach to treatment and ongoing care should be adopted.

DISCUSSION

Implementation of these recommendations

The recommendations have been based on an extensive literature search. In the absence of evidence, statements have been based on the opinion and practice of experts from 12 countries (Czech Republic, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, Turkey, UK and USA). The application of internationally accepted grading criteria prevents us from supporting some of the statements with stronger grades. The project has also led the committee to propose a research agenda for AAV (see box 1). These recommendations have been multidisciplinary with inputs from rheumatologists, internists, renal physicians and also from a clinical immunologist, an otorhinolaryngologist, a chest physician, an ophthalmologist, a vasculitis nurse and a patient with vasculitis. In addition to these recommendations, we have also produced advice on AAV involving the eye and the nose (online supplement) and a lay summary for patients and relatives (online supplement).

Box 1 Research agenda

- Diagnostic and classification criteria for ANCA-associated vasculitis (AAV).
- Identification of biomarkers for AAV.
- Adjunctive plasma exchange–indications for use including serum creatinine cut-off.
- Adequately powered clinical trials of novel biological agents for the treatment of refractory AAV.
- Adequately powered randomised controlled trials in eosinophilic granulomatosis with polyangiitis.
- Long-term outcome studies in AAV.

The previous recommendations were published in 2009 and importantly had a wider remit, covering small and medium vessel vasculitis and not just AAV.[10] Readers are encouraged to refer to them for treatment decisions on: mixed essential cryoglobulinaemic vasculitis (non-viral), the use of antiviral therapy for the treatment of hepatitis C associated cryoglobulinaemic vasculitis and antiviral therapy, PLEX and glucocorticoids for hepatitis B-associated polyarteritis nodosa (PAN). Ultimately the treatment aim of viral-associated cryoglobulinaemic vasculitis should be to treat the underlying viral disease according to current best management strategies.

The current recommendations provide a framework of practice which have updated the previous recommendations and should apply to the majority of patients with AAV. Although once again 15 statements have been formulated; some have been changed and some have been combined: for example there is no longer a separation of glucocorticoids as they are used in conjunction with other immunosuppressive agents. For remission maintenance the voting of the task force reveals that azathioprine is the preferred option over other immunosuppressive agents. In specific situations, where a less aggressive induction regimen has to be preferred—methotrexate or mycophenolate mofetil may be recommended. The task force appreciates that the induction trials involving methotrexate are larger and of higher evidence grade than those using mycophenolate mofetil. We have been explicit in the limited scenarios where methotrexate or mycophenolate mofetil may be justified.

Each statement should be an opportunity for auditing clinical practice (an audit tool has been produced—see online supplement). In addition these current recommendations have produced algorithms which provide clear and concise information for the management of AAV (see figure 1).

These recommendations have also been voted on by the EUVAS membership the results of which are available as a supplementary online file (see online supplement). The results of the EUVAS vote are largely in agreement with the strength of recommendation vote by the task force. There are differences particularly when there are a number of options available and

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the resultant vote may represent the diversity of the EUVAS membership. Importantly task force members who are also members of EUVAS did not vote in the EUVAS survey. Recommendations for clinical management need periodic updating and because of the many advances and ongoing research in this field, this group recommends an update of these recommendations should be conducted in 3 years.

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EXTENDED REPORT

EULAR revised recommendations for the management of fibromyalgia

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ABSTRACT

Objective The original European League Against Rheumatism recommendations for managing fibromyalgia assessed evidence up to 2005. The paucity of studies meant that most recommendations were 'expert opinion'.

Methods A multidisciplinary group from 12 countries assessed evidence with a focus on systematic reviews and meta-analyses concerned with pharmacological/non-pharmacological management for fibromyalgia. A review, in May 2015, identified eligible publications and key outcomes assessed were pain, fatigue, sleep and daily functioning. The Grading of Recommendations Assessment, Development and Evaluation system was used for making recommendations.

Results 2979 titles were identified: from these 275 full papers were selected for review and 107 reviews (and/or meta-analyses) evaluated as eligible. Based on meta-analyses, the only 'strong for' therapy-based recommendation in the guidelines was exercise. Based on expert opinion, a graduated approach, the following four main stages are suggested underpinned by shared decision-making with patients. Initial management should involve patient education and focus on non-pharmacological therapies. In case of non-response, further therapies (all of which were evaluated as 'weak for' based on meta-analyses) should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation programme (for severe disability).

Conclusions These recommendations are underpinned by high-quality reviews and meta-analyses. The size of effect for most treatments is relatively modest. We propose research priorities clarifying who will benefit from specific interventions, their effect in combination and organisation of healthcare systems to optimise outcome.

INTRODUCTION

Fibromyalgia is common with a prevalence of 2% in the general population.[1 2] However, its diagnosis and management remain a challenge for patients and healthcare professionals. It often takes >2 years for a diagnosis to be made with an average of 3.7 consultations with different physicians.[3] Referral to specialists and investigations results in high healthcare use, for up to 10 years prior to diagnosis, compared with persons who do not have fibromyalgia.[4] Although pain is the dominant symptom in fibromyalgia, other symptoms such as fatigue, non-refreshed sleep, mood disturbance and cognitive impairment are common, but not universal, have an important influence on quality of life and emphasise that it is a heterogeneous and complex condition.[5 6]

The original European League Against Rheumatism (EULAR) recommendations for the management of fibromyalgia assessed evidence up to and including 2005.[7] Given the paucity of information and poor quality of the studies available, it was recommended that the guidelines be revised after a period of 4 years. However, no subsequent revision took place and thus a decade later we revisit the recommendations with the aim of making them more evidence based. In the time since the original recommendations, there have been a considerable number of individual trials examining pharmacological and non-pharmacological interventions and, moreover, there have been systematic reviews conducted for nearly all of the commonly used management strategies. Our aim therefore was, using the systematic reviews conducted and taking into account their quality, to make evidence-based recommendations for the use of individual pharmacological and non-pharmacological approaches, and how these could be combined. Further, we aimed to identify priority areas for future research.

METHODS

Working group membership

The working group included 18 members from 12 European countries: clinicians (representing rheumatology, internal medicine, pain medicine and epidemiology), non-clinical scientists (occupational health, epidemiology), patient representatives and the allied health professions (nursing).

Eligibility, search strategy and quality assessment

We focused on systematic reviews (with or without meta-analysis) concerned with the management of fibromyalgia. Details of eligibility, review and quality assessment are provided in online supplementary text.

Evaluating evidence

We retained pain as one of the key outcomes of interest, from the original guidelines, but also included fatigue, sleep and daily functioning. The committee considered the following in making a

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recommendation: number of trials, number of patients, outcomes assessed, quality of reviews and the trials included within the reviews, effect size (and 95% CI), adverse events and cost. We used the Grading of Recommendations Assessment, Development and Evaluation system for making recommendations.[10] This is a four-point scale: strong for/weak for/weak against/strong against; or allowing a recommendation 'use only for research'. The strength of recommendation is based on the balance between desirable and undesirable effects (considering values and preferences), confidence in the magnitude of effects and resource use. A strong recommendation implies that, if presented with the evidence, all or almost all informed persons would make the recommendation for or against the therapy, while a weak recommendation would imply that most people would, although a substantial minority would not.[11]

Two subgroups considered the evidence for pharmacological and non-pharmacological therapies and proposed a recommendation. At a face-to-face meeting, after presentation of the evidence and the preliminary recommendation, discussion resulted in a 'final recommendation'. In addition to the evidence on efficacy/effectiveness, the committee also took into account safety. All participants then voted on their level of agreement with the recommendation on a scale from 0, 'completely disagree', to 10, 'completely agree'. The percentage of the committee scoring at least 7 was taken to indicate level of agreement.

RESULTS

In total, 2979 titles were identified. From these, 571 abstracts and then 275 full papers were selected for review, and 107 reviews evaluated as eligible for consideration in making recommendations for management (figure 1).

Information on the reviews informing these recommendations on pharmacological therapy and on non-pharmacological and complementary and alternative medicines/therapies is collated in online supplementary tables A and B, respectively, while information from one review, for each medicine/therapy, selected based on recency and quality is provided in tables 1 and 2, respectively.

Evaluation of pharmacological medicines

Amitriptyline

Five reviews included up to 13 trials and a maximum of 919 subjects. Häuser *et al*[12] reported that patients receiving amitriptyline were more likely to achieve 30% pain reduction (risk ratio (RR) 1.60, 95% CI 1.15 to 2.24), equivalent to a 'number needed to treat' (NNT) of 3.54, 95% CI 2.74 to 5.01. There was a moderate effect on sleep (standardised mean difference (SMD) −0.56, 95% CI −0.78, to −0.34)[i] and small effect on fatigue (−0.44; −0.71 to −0.16). There was no difference in discontinuation rates compared with patients receiving placebo. Nishishinya *et al*[13] in their high-quality review concluded that 25 mg/day improved pain, sleep and fatigue at 6–8 weeks of treatment but not at 12 weeks while 50 mg/day did not demonstrate efficacy. *Amitriptyline evaluation: weak for, at low dose (100% agreement).*

Anticonvulsants

Nine reviews of pregabalin included up to seven studies and a maximum of 3344 patients. A recent Cochrane review[24] reported patients receiving active treatment were more likely to have 30% pain reduction, RR 1.37, 95% CI 1.22 to 1.53, with a 'number needed to benefit' (NNTB) over placebo of 9, 95% CI 7 to 13. There was a very small effect on fatigue (−0.17; −0.25 to −0.09) and small effect on sleep (−0.35; −0.43 to −0.27) but no effect on disability (−0.01; −0.11 to 0.09). A single, moderate quality, study of gabapentin in 150 subjects (eg, in ref. 104) showed a significant effect on 30% pain reduction (RR 1.65, 95% CI 1.10 to 2.48), a small effect on sleep (−0.71; −1.08 to −0.24) and a large effect on disability (−0.94; −1.32 to −0.56). *Anticonvulsant evaluation: pregabalin—weak for (94% agreement); gabapentin—research only (100% agreement).*

Cyclobenzaprine

A single systematic review of five studies involving 312 patients reported that of those taking cyclobenzaprine 85% experienced side effects and only 71% completed the studies. They were more likely to report themselves as 'improved' (NNT 4.8, 95% CI 3.0 to 11.0). Only two studies reported an 'intention-to-treat' (ITT) analysis. Sleep, but not pain, showed a significant, very small, improvement relative to baseline at the longest outcome considered (12 weeks: SMD 0.34) and patients on placebo showed similar improvement (SMD 0.52).[25] *Cyclobenzaprine evaluation: weak for (75% agreement).*

Growth hormone

A single systematic review of two studies involving 74 patients reported an effect size on pain of 1.36 (0.01 to 1.34).[16] The improvement in functional deficit was not statistically significant (1.24; −0.36 to 2.84). There are concerns on safety (sleep apnoea, carpal tunnel syndrome). The drug is not approved for fibromyalgia (FM) or related disorders in Europe. *Growth hormone evaluation: strong against (94% agreement).*

Monoamine oxidase inhibitors

Four reviews identified up to three studies and 241 patients. Häuser *et al*[26] reported a moderate effect on pain across the studies (−0.54; −1.02, to −0.07), but the single studies that evaluated fatigue and sleep showed no effect. There were no differences in dropouts or adverse events compared with placebo. There was no comparison between compounds. Life-threatening interactions have been documented. *Monoamine oxidase inhibitors (MAOIs) evaluation: weak against (81% agreement).*

NSAIDs

A single review[21] identified two small trials with no evidence of improved outcome compared with placebo. One low-quality review was not considered. *Non-steroidal anti-inflammatory drugs (NSAIDs) evaluation: weak against (100% agreement).*

Serotonin-noradrenalin reuptake inhibitors

Eight systematic reviews were identified, which presented data separately for duloxetine. The largest review of 2249 subjects[32] reported duloxetine, short term (up to 12 weeks) and long term (up to 28 weeks), was more effective than placebo at reducing pain (RR >30% pain, RR 1.38, 95% CI 1.22 to 1.56), although there was no significant effect at 20–30 mg/day and no difference between doses of 60 and 120 mg/day. NNTB, based on 60 mg/day up to 12 weeks, was 6, 95% CI 3 to 12. A previous review reported small effects on sleep (−0.24; −0.37, to −0.12) and disability (−0.33; −0.43, to −0.24) but no effect on fatigue.[30] Seven systematic reviews were identified of milnacipran, a recent one of which evaluated five trials.[30] Patients taking milnacipran were more likely, at the end of treatment, to

[i]All effect sizes are expressed as SMD with 95% CI unless otherwise stated.

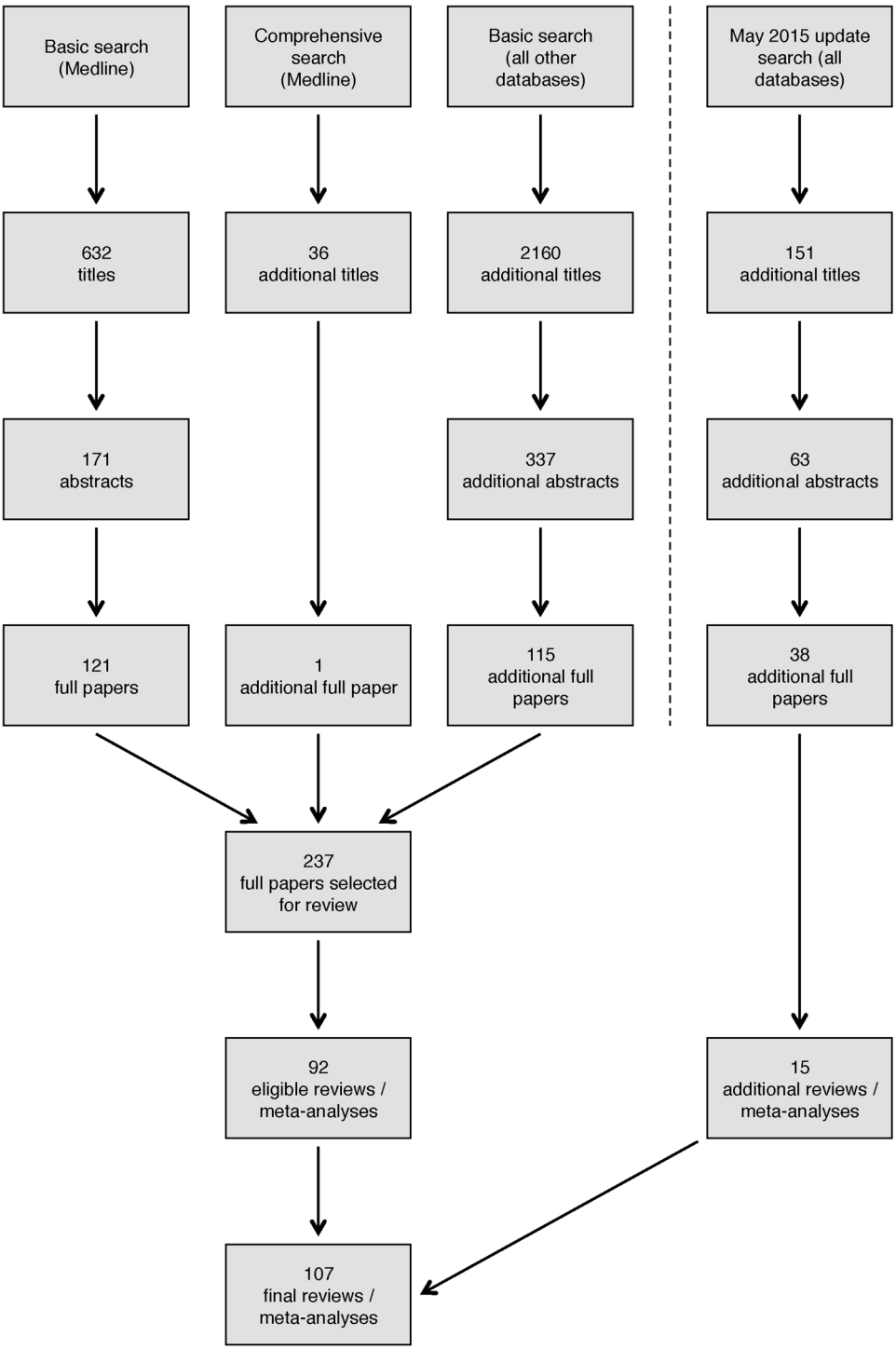

Figure 1 Flow chart identifying eligible reviews.

have 30% pain reduction (RR 1.38, 95% CI 1.25 to 1.51) but there was only a small benefit on fatigue (−0.14; −0.19 to −0.08), disability (−0.16; −0.23 to −0.10) and no effect on sleep. *Duloxetine and milnacipran evaluation: weak for (100% agreement).*

Selective serotonin reuptake inhibitors

Seven systematic reviews included up to 11 trials and a maximum of 521 subjects. Given that reviews have not focused on specific drugs or comparisons, drugs within this class were considered together. A recent review of medium quality included seven trials and reported a moderate effect on pain (−0.40; −0.73, to −0.07), sleep (−0.31; −0.60 to −0.02) and no effect on fatigue (−0.17; −0.46 to 0.11).[36] *Selective serotonin reuptake inhibitor (SSRI) evaluation: weak against (94% agreement).*

Sodium oxybate

A single systematic review of five studies including 1535 patients reported small effects sizes on pain (0.44; 0.31 to 0.58), sleep problems (0.47; 0.28 to 0.66) and fatigue (0.48; 0.35 to 0.60). The European Medicines Agency and the US Food and Drug Administration refused the approval for FM because of safety concerns.[16] The drug is only approved for narcolepsy. *Sodium oxybate evaluation: strong against (94% agreement).*

Table 1 Overview of results from selected systematic reviews of placebo-controlled pharmacological trials

Treatment (review reference)	No. of trials (no. of participants) Review quality	Dosages; durations of treatment	Overall trial quality*	Safety and comments
Amitriptyline[12]	10 (767) AMSTAR=6	10–50 mg/day; 8–24 weeks	Low	There was no analysis of safety but no difference in discontinuation rates compared with patients on placebo was reported.
Anticonvulsants—pregabalin[24]	5 (3256) AMSTAR=10	Three studies with fixed doses of 300, 450 and 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8–14 weeks	High	Increased likelihood of withdrawal due to adverse events, RR 1.68, 95% CI 1.36 to 2.07; NNH 12 95% CI 9 to 17. No difference in likelihood of serious adverse events.
Cyclobenzaprine[25]	5 (312) AMSTAR=7	10–40 mg; 2–24 weeks	Moderate	There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (cyclobenzaprine 29%, placebo 43%). Only two studies conducted ITT.
Growth hormone[16]	2 (74) AMSTAR=5	0.0125 mg/kg/day; adjusted to maintain IGF-1 level of 250 ng/mL after first month, 0.0125 mg/kg/day; 9 months to 1 year	NE	Safety concerns include sleep apnoea and carpal tunnel syndrome.
MAOIs[26]	3 (241) AMSTAR=9	Pirlindole 150 mg/day, moclobemide 150–300 mg/day; 4–12 weeks	Low	MAOIs are known to cause potentially fatal hypertensive crises, serotonin syndrome and psychosis when they interact with foods containing tyramine and medications (many of which are commonly used in the treatment of FM), including SSRIs, tricyclic antidepressants and tramadol. The clinical trials had restrictions on concomitant medications.
NSAIDs[21]	2 (242) AMSTAR=7	Ibuprofen 600 mg four times a day, tenoxicam 20 mg/day; 6–8 weeks	Low	The adverse event profile, although not considered in this review, is well established for this class of drugs.
SNRIs—duloxetine[31]	6 (2249) AMSTAR=10	20–120 mg/day; 12–28 weeks	Moderate	Dropout rates due to side effects across studies higher than with placebo. No difference in serious adverse events.
SNRIs—milnacipran[30]	5 (4118) AMSTAR=10	100 or 200 mg/day; 12–27 weeks	High	Dropout rates due to side effects across studies were double compared with placebo, but there was no difference in serious adverse events.
SSRIs[36]	7 (322) AMSTAR=8	20–40 mg/day citalopram, 20–80 mg/day fluoxetine, 20–60 mg/day paroxetine; 6–16 weeks	Moderate to high	Acceptability and tolerability were similar to placebo NNH 40, 95% CI 19 to 66. Although several studies excluded patients with depression/anxiety, Häuser *et al*[26] showed a small effect of SSRIs in improving depressed mood (SMD −0.37, 95% CI −0.66 to −0.07).
Sodium oxybate[16]	5 (1535) AMSTAR=5	4.5–6 g/day; 8–14 weeks	NE	There is the potential for abuse and central nervous system effects associated with abuse such as seizure, respiratory depression and decreased levels of consciousness.
Tramadol[22]	1 (313) AMSTAR=3	37.5 mg tramadol/325 mg paracetamol 4×/day; 3 months	High	No significant difference in discontinuation due to adverse events (RR 1.62, 95% CI 0.94 to 2.80). A high-quality review (AMSTAR score 7) identified a single study, which, among persons who tolerated and benefitted from tramadol, demonstrated a lower discontinuation rate in a double-blind phase compared with placebo.[21]

*According to the method of quality evaluation used in the review.
AMSTAR, Assessing the Methodological Quality of Systematic Reviews; FM, fibromyalgia; IGF, insulin growth factor; ITT, intention-to-treat; MAOIs, monoamine oxidase inhibitors; NE, not evaluated; NNH, number needed to harm; NSAIDs, non-steroidal anti-inflammatory drugs; RR, risk ratio; SMD, standardised mean difference; SNRI, serotonin-noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Tramadol, a weak opioid with mild serotonin-noradrenalin reuptake inhibitor (SNRI) activity was considered by two reviews. Roskell *et al*[22] identified a single study of tramadol with paracetamol. Those in the active arm were more likely to have 30% improvement in pain (RR 1.77, 95% CI 1.26 to 2.48). *Tramadol evaluation: weak for (100% agreement)*.

The literature search did not identify any reviews on corticosteroids, strong opioids, cannabinoids and antipsychotics. The committee made a 'strong against' evaluation (100% agreement) regarding the use of strong opioids and corticosteroids in patients with fibromyalgia on the basis of lack of evidence of efficacy and high risk of side effects/addiction reported in individual trials.

Evaluation of non-pharmacological therapies; complementary and alternative medicines and therapies

Acupuncture

Eight reviews included up to 16 trials and 1081 participants. One high-quality review included nine trials, with 395 patients, and demonstrated that acupuncture, added to standard therapy, resulted in a 30% (21%, 39%) improvement in pain.[70] Electric acupuncture was also associated with improvements in pain (22%; 4% to 41%) and fatigue (11%; 2% to 20%). Some adverse events were reported, but these were commonly mild and transient. There is little understanding of the active component of acupuncture, and the evidence supporting the use of real versus sham acupuncture was less consistent. *Acupuncture evaluation: weak for (93% agreement)*.

Table 2 Overview of results from selected systematic reviews of non-pharmacological; complementary and alternative medicine and therapy trials

Treatment (review reference)	No. of trials (no. of participants*) Review quality	Dosages; durations of treatment	Overall trial quality†	Safety and comments
Acupuncture[70]	9 (395) AMSTAR=11	Treatment sessions ranged from 3 to 13 weeks (median=4), with needle retention ranging from 20 to 30 min. Only one study provided journal references for the acupuncture point selection, and the description of the type of needle stimulation/ manipulation was clear in only three studies.	Moderate	One in six people who had acupuncture, and one in three controls, reported adverse events. Such events were minor and lasted less than one day. No serious adverse events were reported in any trials.
Biofeedback[92]	7 (321) AMSTAR=8	EMG biofeedback. Individual sessions varied between 45 and 180 min, and the number of sessions varied between 6 and 16. EEG biofeedback. 20–22 sessions of (where reported) 30 min duration.	Poor	Only two‡ trials reported adverse event data. 4% of patients in one trial receiving EMG biofeedback reported stress. And 74% of patients in another, receiving EEG biofeedback reported a variety of side effects, including: headache, fatigue and sleep problems.
Capsaicin[94]	2 (153) AMSTAR=5	Topical application of *Capsicum annuum L*. cream, either 0.025% capsaicin for 4 weeks or 0.075% for 12 weeks.	Not reported	Patients reported moderate, transient, burning or stinging.
Chiropractic[89]	3 (102) AMSTAR=4	Little detail is given for any trials, but treatment elements included massage, stretching, spinal manipulation, education and resistance training.	Low	Around 50% of patients experience mild-to-moderate transient adverse effects after spinal manipulation.§
CBT[57]	23 (2031) AMSTAR=11	Median duration of therapy=10 weeks, with a median number of 10 sessions, and median total hours=18 hours. All but two studies delivered therapy face to face. Median follow-up (where this was performed 17/23 studies)=6 months.	Low	The assessment of safety in most studies was insufficient. Two studies reported dropout due to worsening of comorbid mental disorders. However, CBT is generally considered safe.
Exercise[41]	34 (2276) AMSTAR=9	Exercise programmes lasting 2.5–24 weeks. Aerobic exercise for ≥20 min, once a day (or twice for ≥10 min), 2–3 days a week. Strength training with ≥8 repetitions per exercise, 2–3 times a week.	Moderate	Although patients may initially notice a deterioration in symptoms, exercise is generally considered safe, especially when practised under supervision.
Hydrotherapy/spa therapy[76]	10 (446) AMSTAR=9	Wide variation in precise treatment strategy between trials. Most consisted of water or mud baths at body temperature 36–37°C, or slightly above (40–45°C), with a median treatment time of 240 min (range 200–300), over several weeks.	Low	Three studies reported no side effects of treatment; one reported slight flashes in 10% of the patients. The remaining trials did not explicitly mention safety.
Hypnotherapy[91]	4 (152) AMSTAR=11	Some variation between trials ranging (where reported) from 300 to 420 min, delivered over 10–26 weeks.	Good	Adverse events were not reported in any of the trials.
Massage[63]	9 (404) AMSTAR=7	Massage therapy time lasted 25–90 min, with between 1 and 20 massage sessions in total.	Low to moderate	No adverse events were reported in any of the trials.
Meditative movement[80]	7 (362) AMSTAR=9	Wide variation in treatments between trials, and included yoga, tai chi, qigong or body awareness therapy. Median (range) duration of treatment=16 (6–24) hours, over 4–12 weeks.	Moderate	Although no serious adverse events were reported, six participants (3.1%) withdrew from the trials because of adverse events (increase of pain; muscle inflammation; chlorine hypersensitivity). The review authors concluded that the acceptance and safety of all types of meditative movement therapies were high.
Mindfulness/mind–body therapy[84]	6 (674) AMSTAR=9	Some variation between trials. Single 2–3.5 hours session per week, for 8–10 weeks. Four out of six programmes also included daily home practice (30–45 min) plus a single all-day retreat.	Low	Safety was assessed and reported in none of the trials.
Multicomponent therapy[60]	9 (1119) AMSTAR=9	Enormous variation in treatment strategies between trials. Most included different combinations of exercise (land and/or water based); education; relaxation; and/or some other specific therapeutic component (eg, Tai Chi; or massage).	Moderate	No adverse events were reported in any of the trials.
SAMe[93]	1 (44) AMSTAR=6	400 mg tablet, twice a day, for 6 weeks.	Moderate	Mild adverse effects such as stomach upset and dizziness were reported.
Other: guided imagery[91]	1 (48) AMSTAR=9	Audiotape-led, individual, guided imagery: 30 min daily for 6 weeks recommended. Median of 44 exercises (range 37–136).	Good	Adverse events were not reported.
Other: homeopathy[98]	4 (163) AMSTAR=7	Variation between trials. Two studied individualised homeopathic treatment, consisting of an initial consultation (and treatment), plus follow-up interviews every 4–8 weeks. Two studied *Arnica montana*, *Bryonia alba* or *Rhus toxicodendron* (potency 6c) daily for between 1 and 3 months.	Low to moderate	No information was provided on safety.

*Total number of persons randomised.
†According to the method of quality evaluation used in the review.
‡Elsewhere in the review, it reports that three studies reported on adverse events. However, in the table where these data are presented, it is only clear for two. However, in a third trial, there were no dropouts due to side effects.
§These data were not contained in this review. The initial recommendation for chiropractic was weak against. However, after discussion, this was downgraded to strong against due to potential safety concerns.
CBT, cognitive behavioural therapy; EMG, electromyographic; SAMe, *S*-adenosyl methionine.

Biofeedback

Two reviews included up to seven trials and 307 participants. Glombiewski *et al*[92] reviewed seven studies, comprising 321 participants. Treatment sessions varied from 6 to 22; with control therapy comprising sham biofeedback, attention control, medication and treatment as usual. Biofeedback was effective in reducing pain intensity (Hedges' g=0.79; 0.22 to 1.36), although all trials were poor quality. There was no evidence of effectiveness in terms of fatigue or sleep and subgroup analysis suggested that any effect was limited to electromyographic (0.86; 0.11 to 1.62) rather than electroencephalographic biofeedback (0.71; −0.37 to 1.8). *Biofeedback evaluation: weak against (100% agreement).*

Capsaicin

Two reviews included two trials and 153 participants. The most recent review, a narrative review of two trials, considered data on 153 patients.[94] Both showed some evidence of positive effect in terms of pain relief, although results were not consistent for other outcomes. Capsaicin gel is generally considered safe, although many users report a mild burning sensation when applied to the skin. However, the number of patients and trials was small and was therefore limited in the extent to which they can provide evidence for toxicity. *Capsaicin evaluation: weak against (86% agreement).*

Chiropractic

Three reviews included up to 13 trials and 102 participants. The most recent review summarised three studies.[89] One study was an open pilot study, one quasi-randomised and in the third no between-group differences were observed in terms of pain. The studies were poor quality and lacked robust interpretable data. *Chiropractic evaluation: strong against (93% agreement).*

Cognitive behavioural therapies

Five reviews included up to 30 trials and at least 2031 participants. One high-quality review included 23 trials, comprising >2000 patients, although the quality of individual trials was reported as generally poor.[58] Cognitive behavioural therapies (CBTs) were effective in reducing pain (−0.29; −0.49 to −0.17) and disability (−0.30; −0.51 to −0.08) at the end of treatment compared with a variety of controls groups, and results were sustained long term. *Behavioural therapy evaluation: weak for (100% agreement).*

Exercise

Twenty reviews included up to 34 trials and at least 2494 participants.[ii] The largest, a Cochrane review, considered 47 different exercise interventions.[41] Aerobic exercise was associated with improvements in pain (0.65; −0.09 to 1.39) and physical function (0.66; 0.41 to 0.92). Busch *et al*[42] reviewed five trials with 219 participants and concluded that resistance training resulted in a significant improvement in pain (−3.3 cm on a 10 cm scale; −6.35 to −0.26) as well as function compared with control. There is some consistency with regard to aerobic and strengthening exercises, although insufficient evidence to suggest superiority of one over the other; land and aquatic exercise appear equally effective.[56] *Exercise therapy evaluation: strong for (100% agreement).*

[ii]It is unclear from some of the reviews how many participants were included. The number of participants represents the minimum about which we can be confident.

Hydrotherapy/spa therapy

Four reviews included up to 21 trials and 1306 participants. One high-quality review included 10 trials, 446 participants and compared a median of 4-hour hydrotherapy (range 200–300 min) against various comparators.[76] There was a significant improvement in pain (−0.78; −1.42 to −0.13) at the end of therapy, maintained in the longer term (median 14 weeks), although the review authors noted that no trials conducted an ITT analysis. There was consistency with regard to the evidence for hydrotherapy and balneotherapy, although little evidence to suggest superiority of one over the other.[77] *Hydrotherapy evaluation: weak for (93% agreement).*

Hypnotherapy

One review included four trials, although the number of participants is unclear.[91] Although six trials of hypnotherapy and/or guided imagery were reviewed, only four examined hypnotherapy in isolation. Median treatment duration (where reported) was 360 min and hypnotherapy was compared with a variety of control therapies: cognitive intervention, active control (physical therapy/massage/relaxation/autogenic training) and treatment as usual. A meta-analysis is presented on all six trials, and isolated data for hypnotherapy are not presented. Two of the four hypnotherapy trials report some significant benefit in terms of pain, the other two demonstrate null, non-significant results. *Hypnotherapy evaluation: weak against (86% agreement).*

Massage

Six reviews have been reported and one meta-analysis with nine trials and 404 patients[63] with sessions lasting 25–90 min, and treatment duration ranging from 1 to 24 weeks (median 5 weeks). Comparator treatments included transcutaneous electrical nerve stimulation (TENS), standard care, guided relaxation and acupuncture. Methodological problems were noted with all of the studies, only four were at low risk of bias in terms of random allocation and only two were analysed as ITT. Overall, massage was not associated with a significant improvement in pain (0.37; −0.19 to 0.93), and of the two ITT analyses, one favoured massage and one favoured control (both significant). A subgroup analysis revealed some evidence of a positive effect with massage of ≥5 weeks duration, although this was based solely on lower-quality trials. *Massage evaluation: weak against (86% agreement).*

Meditative movement

Six reviews, including up to eight trials and 559 participants, focused on qigong, yoga, tai chi or a combination of these therapies. However, there was insufficient evidence to make individual recommendations. One review included seven trials, with 362 participants randomised to tai chi, yoga, qigong or body awareness therapy.[80] Total treatment time ranged from 12 to 24 hours and was compared with a variety of controls, including treatment as usual and active control groups (aerobics, wellness education and stretching). At the end of therapy, improvements were seen in sleep (−0.61; −0.95 to −0.27) and fatigue (−0.66; −0.99 to −0.34) some of which were maintained in the longer term. *Meditative movement evaluation: weak for (71% agreement).*

Mindfulness/mind–body therapy

Six reviews included up to 13 trials and 1209 participants. One recent review, a meta-analysis of six trials, with 674 patients[84] provided evidence that mindfulness-based stress reduction

resulted in improvements in pain (−0.23; −0.46 to −0.01) immediately post treatment compared with usual care and compared with active control interventions (−0.44; −0.73 to −0.16). However, these effects were not robust against bias. *Mindfulness/mind–body therapy evaluation*: *weak for (73% agreement)*.

Multicomponent therapy

Two reviews including up to 27 trials and 2407 participants examined the additional benefit of combining therapies compared with individual therapy. Häuser *et al*[60] conducted a review of management involving both educational or psychological therapies and exercise. In a meta-analysis of nine trials and 1119 patients, multicomponent therapy was effective in reducing pain (−0.37; −0.62 to −0.13), and fatigue, immediately post treatment, compared with waiting list, relaxation, treatment as usual and education. However, effects were short-lived. *Multicomponent therapy evaluation: weak for (93% agreement)*.

S-Adenosyl methionine

Two reviews each included one trial with, in combination, 74 participants. De Silva *et al*[93] reported that, after the end of treatment, significant improvements were observed in pain and fatigue compared with placebo. Sim and Adams[52] reviewed a trial comparing *S*-adenosyl methionine (SAMe) with TENS but data on the main trial comparison are omitted. Side effects are usually mild and infrequent. However, the number of patients and trials was small and therefore cannot provide a robust assessment of toxicity and safety. *SAMe evaluation: weak against (93% agreement)*.

Other complementary and alternative therapies

Three reviews of guided imagery included up to six trials and 357 participants. The highest quality, including only one trial, provided some evidence that guided imagery may be effective in reducing pain (−1.52; −2.17 to −0.87).[90] Two reviews of homeopathy included four trials and 163 participants.[97 98] Both contained a review including only four randomised trials, each of which showed some benefit of homeopathy, on some outcomes. However, none of the individual trials were without serious flaws. *Other complementary and alternative therapies (guided imagery, homeopathy): strong against (93% agreement)*.

Reviews were identified that examined electrothermal and phototherapeutic therapy;[99] phytothermotherapy;[100] music therapy, journaling/storytelling[103] and static magnet therapy,[101] although each was insufficient to allow a recommendation. Marlow *et al*[102] examined the effectiveness of transcranial magnetic and/or direct current stimulation. Eight trials included 244 participants, although not all were analysed by ITT, and appropriate group comparisons were not presented for all studies. Overall, there was little evidence to support either therapy, and several studies reported an unacceptably high rate of adverse events and/or discontinuation due to headache.

EULAR revised recommendations

In terms of overall principles, we recommend, based on unanimous expert opinion, that optimal management requires prompt diagnosis and providing the patient with information (including written material) about the condition. There should be a comprehensive assessment of pain, function and the psychosocial context. Management should take the form of a graduated approach with the aim of improving health-related quality of life. It should focus first on non-pharmacological modalities. This is based on availability, cost, safety issues and patient preference.

We have used the evaluation of individual therapies (above) to make 10 specific recommendations, all based on evidence from systematic reviews and all but one from meta-analysis. The recommendations are given in table 3, and a flow chart of how these therapies may be used in management is shown in figure 2.

We were unanimous in providing a 'strong for' recommendation for the use of exercise, particularly given its effect on pain, physical function and well-being, availability, relatively low cost and lack of safety concerns. The available evidence did not allow us to distinguish between the benefits of aerobic or strengthening. We gave 'weak for' recommendations in relation to meditative movement therapies (which improved sleep, fatigue and quality of life) or mindfulness-based stress reduction (which improved pain and quality of life); the physical therapies acupuncture or hydrotherapy for which there was evidence that they improved pain/fatigue and pain/quality of life, respectively. The effects seen in pragmatic trials of such therapies will include specific and non-specific effects, and it is not possible to disentangle these. There were some non-pharmacological therapies we did not recommend because of lack of effectiveness and/or low study quality: biofeedback, capsaicin, hypnotherapy, massage, SAMe and other complementary and alternative therapies. We provided a 'strong against' evaluation for chiropractic based on safety concerns.

In case of lack of effect of the above therapeutic approaches, we recommend individualised treatment according to patient need. Psychological therapies ('weak for') should be considered for those with mood disorder or unhelpful coping strategies: CBT was effective at producing modest, long-term reductions in pain, disability and improving mood. Pharmacological therapies (all 'weak for') should be considered for those with severe pain (duloxetine, pregabalin, tramadol) or sleep disturbance (amitriptyline, cyclobenzaprine, pregabalin). Multimodal rehabilitation ('weak for') programmes should be considered for those with severe disability—in comparison to individual therapies, those that were multimodal improved a range of short-term outcomes. We did not recommend several pharmacological therapies including NSAIDs, MAOIs and SSRIs because of lack of efficacy and specifically gave a 'strong against' evaluation to growth hormone, sodium oxybate, strong opioids and corticosteroids based on lack of efficacy and high risk of side effects.

DISCUSSION

The previous EULAR recommendations provided an important milestone in the management of fibromyalgia. There were nine recommendations, but only three were supported by strong evidence from the scientific literature; most were based on expert opinion. Since that time, there have been a considerable number of trials published addressing issues in the management of fibromyalgia. The availability of systematic reviews and meta-analysis of randomised controlled trials (RCTs) for all the most common approaches to management allowed us to concentrate on these.

Comparison with 2007 EULAR recommendations

Despite the very large increase in the amount of trial data and summarised in meta-analyses, there are no major changes to the approach of managing patients with fibromyalgia, although we provide new evidence in support for some additional non-pharmacological therapies. In addition, all the recommendations are now firmly evidence based. We now recommend that non-pharmacological therapy should be first-line therapy and then if there is a lack of effect that there should be individualised

Table 3 Recommendations

Recommendation	Level of evidence	Grade	Strength of recommendation	Agreement (%)*
Overarching principles				
Optimal management requires prompt diagnosis. Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context. It should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features. In general, the management of FM should take the form of a graduated approach.	IV	D		100
Management of fibromyalgia should aim at improving health-related quality of life balancing benefit and risk of treatment that often requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features (such as depression), fatigue, sleep disturbance and patient preferences and comorbidities; by shared decision-making with the patient. Initial management should focus on non-pharmacological therapies.	IV	D		100
Specific recommendations				
Non-pharmacological management				
Aerobic and strengthening exercise	Ia	A	Strong for	100
Cognitive behavioural therapies	Ia	A	Weak for	100
Multicomponent therapies	Ia	A	Weak for	93
Defined physical therapies: acupuncture or hydrotherapy	Ia	A	Weak for	93
Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction	Ia	A	Weak for	71–73
Pharmacological management				
Amitriptyline (at low dose)	Ia	A	Weak for	100
Duloxetine or milnacipran	Ia	A	Weak for	100
Tramadol	Ib	A	Weak for	100
Pregabalin	Ia	A	Weak for	94
Cyclobenzaprine	Ia	A	Weak for	75

*Percentage of working group scoring at least 7 on 0–10 numerical rating scale assessing agreement.

therapy according to patient need, which may include pharmacological therapy.

Comparison with other recommendation

There are three recent guidelines on the management of FM from Canada, Israel and Germany that have been compared with respect to their recommendations.[105] These guidelines and our EULAR recommendations are in agreement on the principles of approach to management, the need for tailored therapy to the individual and the first-line role of non-pharmacological therapies. There are differences between our guidelines and previous guidelines, which can partly be explained by us using more recently available evidence. There are differences in the strength of recommendations relating to pharmacological therapies: anticonvulsants and SNRIs were strongly recommended by the Canadian and Israeli guidelines while the German and these EULAR guidelines provide a weak recommendation. There are also differences in relation to individual non-pharmacological therapies across guidelines in terms of whether they were assessed. For example, meditative movement is strongly recommended by the German guidelines, but recommended only for a minority of patients in Israel, while these EULAR guidelines provide a 'weak for' recommendation.

The committee recommended that an update is conducted after 5 years in order to determine whether for those therapies with relatively little current evidence further trials have been conducted and, second, whether any new therapies have emerged for the management of fibromyalgia.

Research priorities

In the course of discussion, we identified important questions in terms of guiding management where there was either insufficient (or often no) evidence base to guide decisions, that is, 'research gaps'. We discussed their relatively priority taking into account their potential to guide management, the likelihood that such studies could be conducted and were likely to be funded. We identified five such priority questions:

- Which type of exercise is most effective: strength and/or aerobic training?
- Are combined pharmacological and non-pharmacological approaches to management more effective than single-modality management?
- Are there characteristics of patients with fibromyalgia that predict response to specific therapies?
- How should fibromyalgia be managed when it occurs as a comorbidity to inflammatory arthritis?
- What aspects of a healthcare system optimise outcome for patients (who is best for the management of FM patients)?

Some of these questions are best answered by RCTs. Given, however, the expense of such studies and that they can take almost 10 years from identifying the questions to be answered to results being obtained, alternatives including registers and observational studies should be considered. These can be complemented by qualitative studies to determine the needs of patients.

Dissemination

These recommendations will be disseminated by the international working group through national rheumatology societies. This will include scientific meetings, newsletters and continuing education programmes. We will produce a summary of the recommendations suitable for dissemination through EULAR-affiliated patient groups and through national patient societies. We will investigate assessing agreement with the recommendations in the target population.

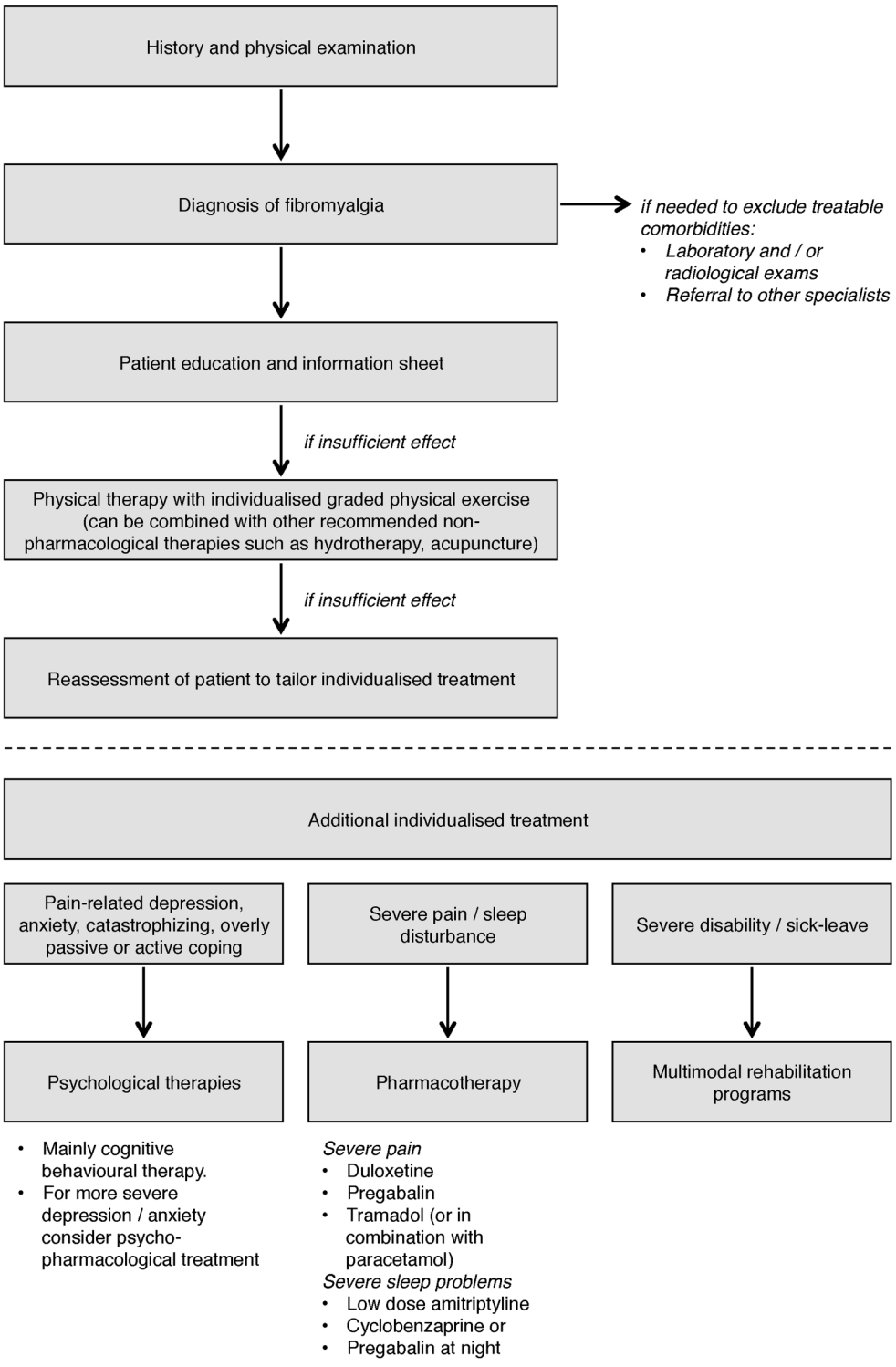
History and physical examination
Diagnosis of fibromyalgia
if needed to exclude treatable comorbidities:
• Laboratory and / or radiological exams
• Referral to other specialists
Patient education and information sheet
if insufficient effect
Physical therapy with individualised graded physical exercise (can be combined with other recommended non-pharmacological therapies such as hydrotherapy, acupuncture)
if insufficient effect
Reassessment of patient to tailor individualised treatment
Additional individualised treatment
Pain-related depression, anxiety, catastrophizing, overly passive or active coping
Severe pain / sleep disturbance
Severe disability / sick-leave
Psychological therapies
Pharmacotherapy
Multimodal rehabilitation programs
• Mainly cognitive behavioural therapy.
• For more severe depression / anxiety consider psycho-pharmacological treatment
Severe pain
• Duloxetine
• Pregabalin
• Tramadol (or in combination with paracetamol)
Severe sleep problems
• Low dose amitriptyline
• Cyclobenzaprine or
• Pregabalin at night

Figure 2 Management recommendations as flow chart.

SUMMARY

In summary, these revised EULAR recommendations newly incorporate a decade of evidence in relation to the pharmacological and non-pharmacological management of fibromyalgia. They allow EULAR to move from recommendations that are predominantly based on expert opinion to ones that are firmly based on scientific evidence from high-quality reviews and meta-analyses. Despite this evidence, however, the size of effect for many treatments is relatively modest. We propose focusing on the research priorities we outline to address issues clarifying to whom certain interventions may best be delivered, their effect in combination, matching patients to therapies and the organisation of healthcare systems to optimise outcome.

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2016 updated EULAR evidence-based recommendations for the management of gout

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ABSTRACT

Background New drugs and new evidence concerning the use of established treatments have become available since the publication of the first European League Against Rheumatism (EULAR) recommendations for the management of gout, in 2006. This situation has prompted a systematic review and update of the 2006 recommendations.

Methods The EULAR task force consisted of 15 rheumatologists, 1 radiologist, 2 general practitioners, 1 research fellow, 2 patients and 3 experts in epidemiology/methodology from 12 European countries. A systematic review of the literature concerning all aspects of gout treatments was performed. Subsequently, recommendations were formulated by use of a Delphi consensus approach.

Results Three overarching principles and 11 key recommendations were generated. For the treatment of flare, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), oral or intra-articular steroids or a combination are recommended. In patients with frequent flare and contraindications to colchicine, NSAIDs and corticosteroids, an interleukin-1 blocker should be considered. In addition to education and a non-pharmacological management approach, urate-lowering therapy (ULT) should be considered from the first presentation of the disease, and serum uric acid (SUA) levels should be maintained at<6 mg/dL (360 μmol/L) and <5 mg/dL (300 μmol/L) in those with severe gout. Allopurinol is recommended as first-line ULT and its dosage should be adjusted according to renal function. If the SUA target cannot be achieved with allopurinol, then febuxostat, a uricosuric or combining a xanthine oxidase inhibitor with a uricosuric should be considered. For patients with refractory gout, pegloticase is recommended.

Conclusions These recommendations aim to inform physicians and patients about the non-pharmacological and pharmacological treatments for gout and to provide the best strategies to achieve the predefined urate target to cure the disease.

INTRODUCTION

Gout is a disabling and common disease in Europe; its prevalence ranges from 0.9% to 2.5% depending on the country.[1–3] The prevalence and incidence of the disease have increased steadily in recent years, particularly in the UK.[4 5] However, despite effective treatments, gout is still often misdiagnosed and its management remains suboptimal.[3 6 7] This situation prompted the elaboration of the first European League Against Rheumatism (EULAR) recommendations for the management of gout, in 2006, which were based on a systematic literature review (SLR) and expert opinion.[8]

Since 2006, our knowledge of the pathophysiology of the disease has improved greatly[9 10] and the field of gout management has advanced quickly. When the first EULAR recommendations were produced, the number of drugs available for gout treatment was limited and the main urate-lowering therapy (ULT) was allopurinol. Since then, a number of new drugs have become available or are in late-stage development (ie, febuxostat, pegloticase, interleukin-1 (IL-1) blockers, lesinurad).[11 12] Moreover, additional data on established drugs such as colchicine[13] and allopurinol[14–16] have been published, and studies have repeatedly identified increased cardiovascular mortality with gout.[17]

Therefore, the indications for old and new drugs need to be clarified and novel therapeutic strategies recommended on the basis of their availability, the patient profile, previous drug failure and benefit/risk ratio as well as the cost of the various drugs now available for the treatment of flare and for lowering urate levels. For this purpose, a task force was convened to update the 2006 EULAR recommendations for the management of gout, with the objective of addressing all overarching principles and individual recommendations by a SLR and expert and patient opinion.

METHODS

With the approval of the EULAR executive committee, the convenor (TB) along with two co-convenors of the 2006 task force (MD and EP), an epidemiologist (FT) and an academic rheumatologist (PR) formed a steering group to update the 2006 EULAR recommendations for the management of gout. The steering group prioritised the research questions, drafted the methodology to be used for these novel set of recommendations and assembled a task force.

This EULAR task force comprised 15 rheumatologists, 1 musculoskeletal radiologist, 2 general practitioners (GPs), 1 research fellow, 2 patients and 3 experts in epidemiology/methodology from 12 European countries. The recommendations were developed according to the standardised operating procedures for the elaboration, evaluation

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dissemination and implementation of recommendations endorsed by the EULAR.[18 19]

The first step was to determine whether the 12 former EULAR recommendations (2006) for the management of gout should be retained, modified or abandoned. For this purpose, members of the task force were sent a questionnaire and were asked to rate each recommendation by using a 9-point numerical rating scale (1, totally disagree; 9, fully agree). For each item, participants indicated whether they would keep the same recommendation (first question). If the answer was scored ≥5, the participants were then asked if they would modify the recommendation (second question). It was explained that the phrasing of the updated recommendations should not be a mere clinical statement—as for most of the 2006 EULAR recommendations—but wherever possible should take the form of a clear active recommendation specific to a particular clinical situation, as advised by the Appraisal of Guidelines for Research & Evaluation (AGREE II).[20] The steering group had predetermined that an item from the 2006 recommendations would be deleted if all scores from the participants for the first question were <5 with a median ≤3.5. Conversely, the item would be unchanged if all scores for to the first question were ≥5 with a median ≥7 and when all scores for the second question were <5 with a median ≤3.5. If not, the items had to be modified. Members of the task force were also invited to indicate topics they would like to address for additional recommendations.

Subsequently, one research fellow (JC-S) with the help of an expert in systematic review methodology (SG) performed an SLR by searching for literature published since 1 January 2005 in MEDLINE, EMBASE and Cochrane Library databases in June 2013. This process included both a general search and a proposition-specific search. The general search strategy consisted of two basic components: (1) gout in whatever possible terms in the databases and (2) types of study design in the forms of systematic review/meta-analysis, randomised controlled trial (RCT)/controlled trial, uncontrolled trial, cohort study, case–control study, cross-sectional study. The two components were combined to search for the current available research evidence on gout. The quality of evidence and grades of recommendation were determined according to the standards of the Oxford Centre for Evidence-Based Medicine.[19] The quality of evidence was assessed by the GRADE method. Criteria for RCTs included adequate randomisation and allocation concealment, prognostic similarity between groups (in terms of the evaluated outcome), equal follow-up of groups, adequate blinding, validation of outcomes, application of intent-to-treat analysis, selective outcome reporting, stopping early for benefit, α-risk control with multiple comparisons or multiple outcomes. Criteria for observational studies included choice of controls, measurement of both exposures and outcomes, confounding factors, completeness of data, magnitude of effect and dose–response gradient. Criteria for meta-analysis included a priori-defined objectives and outcomes of interest, description of the literature search, selection criteria for included studies, assessment of quality of studies, evaluation of publication bias and homogeneity of results.

In the next step, all task force members attended a 2-day meeting during which results of the SLR were presented in an aggregated form. The task force debated and evaluated the evidence presented and formulated a preliminary set of new recommendations. Then, the task force reached consensus regarding the proposed recommendations by using the Delphi sequential voting technique by email after the meeting. Subsequently, the level of agreement for each recommendation was graded. Each participant was asked to rate each recommendation again by using the 9-point numerical rating scale (1, totally disagree; 9, fully agree) and could propose a reformulation of the recommendation.

Subsequently, this set of recommendations was externally evaluated by GPs (n=8) and rheumatologists (n=5) mainly in independent or private practice in Europe (the UK, The Netherlands, Spain, France, Portugal and Italy). Each physician was asked to rate each recommendation by using the abovementioned numerical rating scale. Finally, the task force set up a research agenda to discuss and develop 14 proposals.

Finally, because the delay between the first SLR and the writing of the present manuscript was longer than expected, we conducted an additional SLR from June 2013 to May 2016. Results from this updated SLR can be found in the online supplementary material. The steering group discussed result of this SLR and agreed that it did not impact the overall content of the whole recommendations. Relevant references have been inserted in the body of the manuscript.

RESULTS

The task force voted unanimously for a change in all items of the 2006 recommendations (see online supplementary material). Therefore, all the previous recommendations were amended to reflect newly available evidence from the SLR. In total, 984 references were retrieved form the literature search, among which 51 were analysed (see flow chart, online supplementary material).

At the end of the 2-day meeting, a set of 14 preliminary new recommendations was produced and three Delphi rounds by email were needed to establish the final set of recommendations. Because too many recommendations might result in a loss of focus, the steering committee decided to move the first three recommendations under the umbrella of 'overarching principles', for a final set of 11 novel recommendations that focus more specifically on the treatment of flares and long-term management (tables 1 and 2). The external evaluation is provided as online supplementary material, and the research agenda appears in box 1.

Overarching principles

A. *Every person with gout should be fully informed about the pathophysiology of the disease, the existence of effective treatments, associated comorbidities and the principles of managing acute attacks and eliminating urate crystals through lifelong lowering of SUA below a target level.*

Although gout is a curable disease, its management is still not optimal in a large proportion of patients.[6] Recent studies report that less than half of the patients with gout receive ULT, and that when prescribed, it is often at an insufficient dose to effectively lower the SUA levels to target.[21–24] Since the last 2006 recommendations, barriers to the effective treatment and cure of gout have been identified and the importance of the lack of knowledge of the disease and subsequent non-adherence to treatment have been emphasised.[25–27] Moreover, an observational study showed that full patient education increased adherence to ULT, leading to a high rate (92%) of effectively treated patients at 12 months.[28]

Education of patients was mentioned in the 2006 recommendation (item 2) together with general advice regarding lifestyle as part of a global recommendation. With this first overarching principle dedicated solely to education, the task force emphasises that education is a key aspect of gout management. Also it introduces the approach 'treat to serum urate target,' which has been found effective in alleviating all features of the disease.[28]

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Table 1 Overarching principles and final set of 11 recommendations for the treatment of gout

	Overarching principles
A	Every person with gout should be fully informed about the pathophysiology of the disease, the existence of effective treatments, associated comorbidities and the principles of managing acute attacks and eliminating urate crystals through lifelong lowering of SUA level below a target level.
B	Every person with gout should receive advice regarding lifestyle: weight loss if appropriate and avoidance of alcohol (especially beer and spirits) and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged. Regular exercise should be advised.
C	Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout.
	Final set of 11 recommendations
1	Acute flares of gout should be treated as early as possible. Fully informed patients should be educated to self-medicate at the first warning symptoms. The choice of drug (s) should be based on the presence of contraindications, the patient's previous experience with treatments, time of initiation after flare onset and the number and type of joint(s) involved.
2	Recommended first-line options for acute flares are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus proton pump inhibitors if appropriate), oral corticosteroid (30–35 mg/day of equivalent prednisolone for 3–5 days) or articular aspiration and injection of corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. Colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin.
3	In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroid (oral and injectable), IL-1 blockers should be considered for treating flares. Current infection is a contraindication to the use of IL-1 blockers. ULT should be adjusted to achieve the uricaemia target following an IL-1 blocker treatment for flare.
4	Prophylaxis against flares should be fully explained and discussed with the patient. Prophylaxis is recommended during the first 6 months of ULT. Recommended prophylactic treatment is colchicine, 0.5–1 mg/day, a dose that should be reduced in patients with renal impairment. In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine. Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided. If colchicine is not tolerated or is contraindicated, prophylaxis with NSAIDs at low dosage, if not contraindicated, should be considered.
5	ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. ULT is indicated in all patients with recurrent flares, tophi, urate arthropathy and/or renal stones. Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years) or with a very high SUA level (>8.0 mg/dL; 480 μmol/L) and/or comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure). Patients with gout should receive full information and be fully involved in decision-making concerning the use of ULT.
6	For patients on ULT, SUA level should be monitored and maintained to <6 mg/dL (360 μmol/L). A lower SUA target (<5 mg/dL; 300 μmol/L) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout. SUA level <3 mg/dL is not recommended in the long term.
7	All ULTs should be started at a low dose and then titrated upwards until the SUA target is reached. SUA <6 mg/dL (360 μmol/L) should be maintained lifelong.
8	In patients with normal kidney function, allopurinol is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricaemia target. If the SUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated.
9	In patients with renal impairment, the allopurinol maximum dosage should be adjusted to creatinine clearance. If the SUA target cannot be achieved at this dose, the patient should be switched to febuxostat or given benzbromarone with or without allopurinol, except in patients with estimated glomerular filtration rate <30 mL/min.
10	In patients with crystal-proven, severe debilitating chronic tophaceous gout and poor quality of life, in whom the SUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated.
11	When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible; for hypertension consider losartan or calcium channel blockers; for hyperlipidaemia, consider a statin or fenofibrate.

IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; SUA, serum uric acid; ULT, urate-lowering therapy.

B. Every person with gout should receive advice regarding lifestyle: weight loss if appropriate and avoidance of alcohol (especially beer and spirits) and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged. Regular exercise should be advised.

Since the previous recommendations (item 2), several studies have confirmed that weight loss, achieved by dietary intervention or bariatric surgery[29–32] is effective in reducing SUA level. Moreover, regular physical activity might decrease the excess mortality associated with chronic hyperuricaemia.[33]

In addition, the association between excessive intake of meat and alcohol with an increased risk of developing gout has been confirmed[29 34 35] as well as increased risk of gout attacks.[36 37]

Importantly, other modifiable risk factors have been identified since 2006, specifically sugar-sweetened drinks, foods rich in fructose and orange or apple juice.[38–41] In contrast, according to epidemiological studies, consumption of coffee,[42–44] and cherries is negatively associated with gout, and eating cherries may reduce the frequency of acute gout flares.[45] Studies found an inverse association between dairy intake and urate levels, particularly with skimmed milk and low-calorie yoghurt.[34 46] This likely results from the uricosuric property of milk, as demonstrated in an RCT.[47] The benefit of dairy products, underlined in the 2006 recommendation, was reported in a RCT, suggesting that skimmed milk powder derivatives have anti-inflammatory effects against acute gout flares.[48] However, impact of lifestyle and dietary modification has little effect on urate concentrations.[49 50] In addition, the task force recognises that the level of evidence to support the effect of lifestyle modification on SUA levels is low, and therefore, this overarching principle was mainly based on expert opinion. However, given the high prevalence of cardiovascular comorbidities in patients with gout, lifestyle modifications should also be implemented as part of cardiovascular prevention.

C. Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout.

The importance of screening and managing hypertension, hyperglycaemia and obesity in patients with gout was addressed in the previous recommendations (item 3). Since then, a

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Table 2 Evidence, grade of recommendation and level of agreement for each recommendation

Item	Category of evidence	Grade of recommendation	Level of agreement (mean±SD)
A	NA	NA	8.9±0.3
B	NA	NA	8.4±1.1
C	NA	NA	8.5±0.9
1	1b*, 4	A, D	8.4±1.1
2	1b, 3†	A, C	8.6±0.7
3	1b‡, 3§	A, C	8.1±0.9
4	2b	B	8.1±0.9
5	1b	A	8.2±0.9
6	3	C	8.8±0.5
7	3	C	8.6±0.7
8	1b¶, 2b**	A, B	8.8±0.4
9	3	C	8.8±0.4
10	1b	A	8.2±1.3
11	3	C	8.2±0.9

Ranking for category of evidence and grade of recommendation is provided in the online supplementary material.
*For the evidence that colchicine should be given as early as possible, within 12 hours of symptom onset.
†There are no randomised controlled trials of intra-articular corticosteroid injections for flares.
‡Level of evidence for canakinumab.
§For ankinra.
¶Level of evidence for febuxostat and allopurinol.
**For uricosurics (probenecid or benzbromarone).
NA, not applicable.

Box 1 Proposals for future research

- Investigating the ability of low-dose NSAIDs or prednisone to prevent ULT-induced flares.
- A head-to-head trial of anakinra versus a conventional anti-inflammatory agent for the treatment of flares.
- A controlled trial of early low-dose colchicine versus early NSAIDs or oral corticosteroids or potential new drugs for flares over 1 week.
- The optimal combined therapy for treatment of an acute attack.
- The optimal duration for prophylaxis of acute attacks when starting ULT.
- Risk factors for flares when initiating ULT.
- The long-term impact of very low urate levels on the central nervous system.
- The possible benefits of XO inhibition and/or lowering serum uric acid levels for cardiovascular diseases.
- The impact of ULT on kidney function.
- The best strategy in patients with tophaceous gout.
- Direct comparison (efficacy, side effects, cost utility) between emerging uricosurics and allopurinol or febuxostat.
- The cost-utility of HLA-B*58:01 determination before initiating allopurinol in patients not of Asian descent.
- Imaging to visualise crystal dissolution during ULT.
- More research should be conducted in primary care.

NSAID, non-steroidal anti-inflammatory drug; ULT, urate-lowering therapy.

number of studies have demonstrated that both hyperuricaemia and gout are associated with chronic kidney disease (CKD).[51 52] In a US population-based study, the prevalence of CKD (stage ≥2) in patients with SUA level ≥10 mg/dL (594.9 µmol/L) and in patients with gout was 86% and 53%, respectively. CKD appears to be a major risk factor for gout and, conversely, gout might cause renal dysfunction.[53 54] The task force agreed that identifying CKD in patients with gout was of major importance because of the therapeutic implications, as discussed in items 1, 2, 4, 5, 8 and 9. Therefore, estimated glomerular filtration rate (eGFR) should be calculated at the time of diagnosis for CKD classification and monitored regularly in parallel with SUA measurement. This item also emphasises the need to search for other important associated comorbidities, especially coronary heart disease, heart failure, stroke, peripheral arterial disease and diabetes because large epidemiological studies have suggested that hyperuricaemia and/or gout are independent risk factors for these conditions[55–63] and for death due to cardiovascular causes.[17 58]

Final set of 11 recommendations on treating patients with gout

1. *Acute flares of gout should be treated as early as possible. Fully informed patients should be educated to self-medicate at the first warning symptoms. The choice of drug(s) should be based on the presence of contraindications, the patient's previous experience with treatments, time of initiation after flare onset and the number and type of joint(s) involved.*

This recommendation was mainly based on expert opinion and derives from the first item of the 2006 recommendations. Because of the recognised high frequency of comorbidities and thus the high frequency of comedications in patients with gout, the task force felt that a global recommendation regarding the choice of drugs for flares based on the presence or absence of contraindications was highly desirable. This item emphasises the importance of searching for contraindications, often present in patients with gout. One study found that more than 90% of patients had at least one contraindication to non-steroidal anti-inflammatory drugs (NSAIDs) and that about one-third of patients who were prescribed colchicine had at least one major contraindication.[64] This item also underlines the importance to treat as early as possible. Colchicine is effective when given within 12 hours of symptoms onset[13] and there was general agreement that early initiation of any treatment for flare leads to better effectiveness. Therefore, the task force recommends the 'pill in the pocket' approach to treat flare in fully informed patients.

2. *Recommended first-line options for acute flare are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus a proton pump inhibitor if appropriate), oral corticosteroids (30–35 mg/day of equivalent prednisolone for 3–5 days) or articular aspiration and injection of corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. Colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin.*

This item amalgamates the 2006 items 4–6, which have been amended in light of novel evidence. The main therapeutic options for flare are colchicine, NSAIDs and corticosteroids. The task force does not prioritise between these options because of no direct comparative evidence, but unlike 2006 item 4, it recommends considering combination therapy, such as colchicine and an NSAID or colchicine and corticosteroids, which can be proposed for patients with particularly severe acute gout (figure 1), for instance, when flares involve multiple

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joints. In comparison to 2006 items 4 and 5, more evidence is now available in terms of the effectiveness of colchicine,[65] NSAIDs[66–69] and oral corticosteroids.[70–72] A double-blind, randomised equivalence trial of crystal-proven gout from a primary care source population found that prednisolone (35 mg/day for 5 days) was equivalent to naproxen (500 mg twice a day for 5 days) for treating flare.[71 72] A recent trial also found that oral prednisolone (30 mg/day for 5 days) had analgesic effectiveness equivalent to that of indomethacin.[70] The AGREE trial demonstrated that when taken within 12 hours of flare onset, self-administrated low-dose colchicine (1.8 mg) was as effective as high-dose colchicine (4.8 mg) but with a safety profile comparable to that of a placebo.[65] In Europe, colchicine is available in 1 mg tablets, so the task force recommends the use of 1 mg colchicine followed 1 hour later by 0.5 mg for treating flare. A pharmacokinetic study[73] showed that strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin, clarithromycin, verapamil and ketoconazole when prescribed with colchicine increased colchicine plasma concentration, thereby exposing patients to risk of serious side effects. The safe use of colchicine in patients with severe renal impairment (GFR <30 mL/min) has not been established. Because colchicine clearance is decreased in patients with severe renal impairment,[74 75] the group considered that it should be avoided in these patients, because a reduced dosage[73] might be a source of therapeutic misuse. In addition, it should be noted that colchicine is

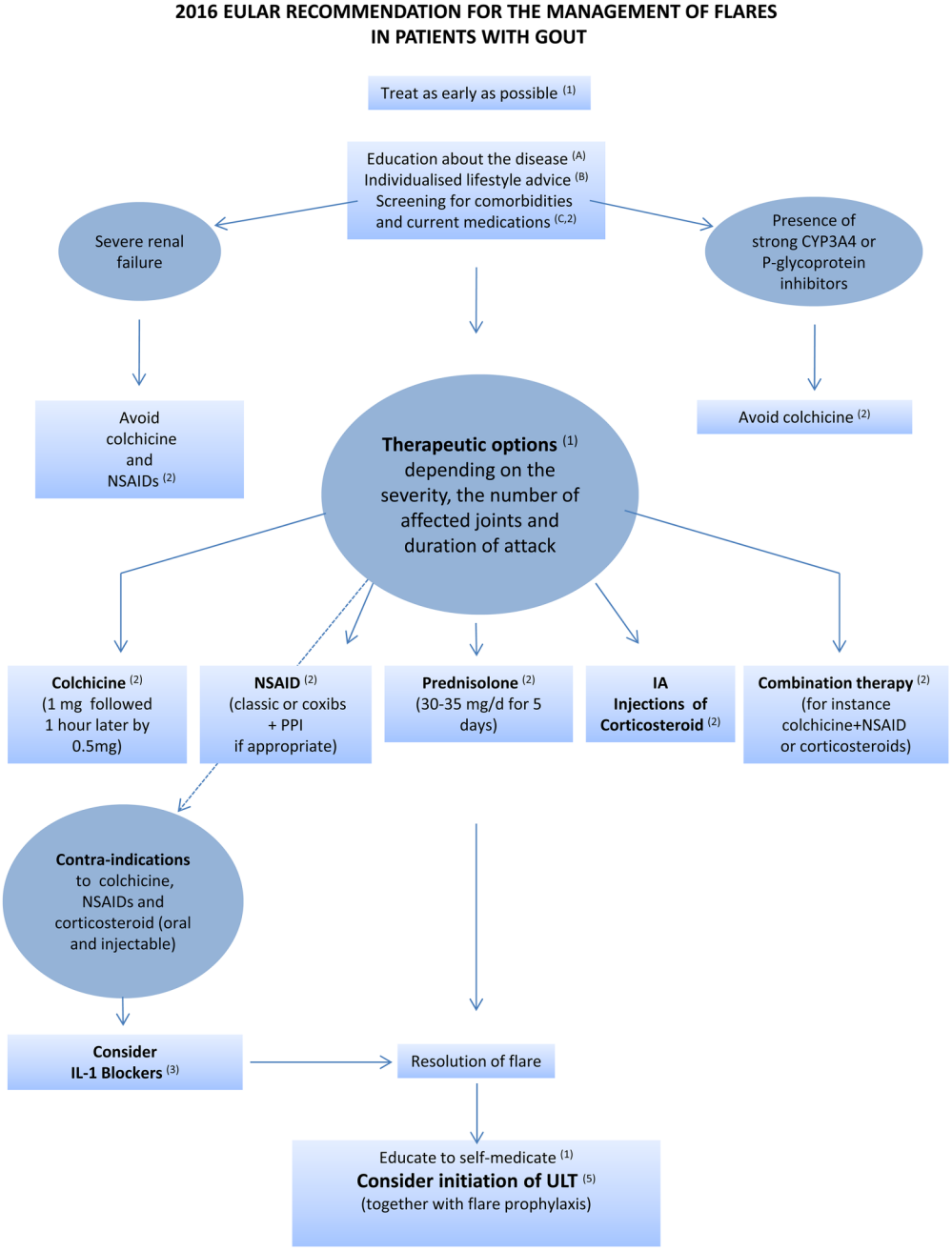
2016 EULAR RECOMMENDATION FOR THE MANAGEMENT OF FLARES IN PATIENTS WITH GOUT
Treat as early as possible (1)
Education about the disease (A)
Individualised lifestyle advice (B)
Screening for comorbidities and current medications (C,2)
Severe renal failure
Presence of strong CYP3A4 or P-glycoprotein inhibitors
Avoid colchicine and NSAIDs (2)
Avoid colchicine (2)
Therapeutic options (1) depending on the severity, the number of affected joints and duration of attack
Colchicine (2) (1 mg followed 1 hour later by 0.5mg)
NSAID (2) (classic or coxibs + PPI if appropriate)
Prednisolone (2) (30-35 mg/d for 5 days)
IA Injections of Corticosteroid (2)
Combination therapy (2) (for instance colchicine+NSAID or corticosteroids)
Contra-indications to colchicine, NSAIDs and corticosteroid (oral and injectable)
Consider IL-1 Blockers (3)
Resolution of flare
Educate to self-medicate (1)
Consider initiation of ULT (5)
(together with flare prophylaxis)

Figure 1 Management of acute flare according to the European League Against Rheumatism recommendations. Letters and numbers in parentheses indicate the items of the recommendations presented in table 1. Strong P-glycoprotein or CYP3A4 inhibitors are cyclosporin, clarithromycin, ketoconazole and ritonavir. IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; ULT, urate-lowering therapy.

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contraindicated in some countries in patients with severe renal failure. From data from two RCTs,[71 72] the group also recommends the use of oral prednisolone at 30–35 mg for 5 days for treating flare. Finally, from data from an open trial[76 77] and expert opinion, the group considered that intra-articular injection of corticosteroids, which has a good safety profile, should be considered particularly in patients with monoarthritis of an easily accessible joint, although acknowledging that this may not be practical in many primary care settings.

3. *In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroids (oral and injectable), IL-1 blockers should be considered for treating flares. Current infection is a contraindication to the use of IL-1 blockers. ULT should be adjusted to achieve the uricaemia target following IL-1 blocker treatment for flare.*

Since the last 2006 recommendations, IL-1β was found to play a crucial role in monosodium urate (MSU) crystal-induced inflammation.[78] Two RCTs have reported that the anti-IL-1β monoclonal antibody canakinumab (150 mg subcutaneously, one dose) was superior to triamcinolone acetonide (40 mg subcutaneously, one dose) in reducing pain in patients with flare with contraindication, intolerance of or non-response to NSAIDs and/or colchicine.[79] These findings led to approval of the drug in Europe solely in patients with contraindication to colchicine, NSAIDs and steroids. Despite the lack of RCTs of anakinra, a case series also suggest that this IL-1 receptor antagonist, administered subcutaneously at 100 mg for 3 days, could be effective in reducing pain in patients with acute attacks.[80–83] By contrast, an RCT demonstrated that one subcutaneous injection of rilonacept, 320 mg, a soluble receptor fusion protein binding both IL-1α and IL-1β,[84] provided no benefit over indomethacin (oral, 50 mg, three times a day for 3 days).[85] Because of the risk of sepsis in patients receiving IL-1 blockers,[86] the task force considered current infection a contraindication to the use of anti-IL-1 biologics, which implies screening for occult infections. Finally, in accordance with the European Medicines Agency labelling of canakinumab, the group stressed the need to effectively lower SUA level in these patients with severe gout once the flare resolved following IL-1β blockade.

4. *Prophylaxis against flares should be fully explained and discussed with the patient. Prophylaxis is recommended during the first 6 months of ULT. Recommended prophylactic treatment is colchicine, 0.5–1 mg/day, a dose that should be reduced in patients with renal impairment. In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine. Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided. If colchicine is not tolerated or is contraindicated, prophylaxis with NSAIDs at a low dosage, if not contraindicated, should be considered.*

Dispersion of MSU crystals during the initial phase of deposit dissolution may expose the patient to increased rate of acute flare that can contribute to poor treatment adherence.[87] The 2006 recommendations (item 11) mentioned that prophylactic treatment should be given during the first months of ULT. Since then, data from pivotal trials of febuxostat versus a fixed dose of allopurinol (300 mg) found that flare prophylaxis with low-dose colchicine (colchicine, 0.6 mg/day) or low-dose NSAID (naproxen, 250 mg twice daily) for up to 6 months appeared to provide greater benefit than flare prophylaxis for 8 weeks, with no increase in adverse events.[88] However, the task force felt that initiation of prophylaxis should be discussed with every patient. Indeed, a study found that following patient education and with slow upward titration of ULT, mostly allopurinol, many patients chose not to take prophylaxis and did not experience a significantly greater flare rate.[28] This recommendation also explicitly underlines the need to search for renal impairment before prescribing colchicine[75] and co-prescription with statins[89] and P-glycoprotein and/or CYP3A4 inhibitors[73] to avoid serious side effects. Of note, two RCTs found that low-dose colchicine in patients with a history of coronary heart disease could reduce the incidence of major cardiovascular events.[90 91] Reports for several trials described the efficacy of canakinumab and rilonacept,[92–96] two IL-1 inhibitors, for preventing flares during the initiation of allopurinol therapy. However, none of them has been approved for prophylactic treatment.

5. *ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. ULT is indicated in all patients with recurrent flare (≥2/year), tophi, urate arthropathy and/or renal stones. Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years), or with a very high SUA level (>8 mg/dL; 480 µmol/L) and/or comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure). Patients with gout should receive full information and be fully involved in decision-making concerning the use of ULT.*

ULT allows for dissolving crystal deposits and the disappearance of gout features, as long as uricaemia is maintained to target. Since 2006, large trials have shown that appropriate ULT reduces the frequency of gout flare and once all crystals have been dissolved, avoids their reoccurrence.[97–99] In addition, effective ULT reduces the size and number of tophi[97 99 100] and facilitates their disappearance, thereby improving the quality of life of patients with gout,[101 102] which can be seriously impaired by the disease.[103–106]

Several studies concur in showing that gout is a risk factor for mortality, in particular from cardiovascular causes,[17 107 108] and a risk factor for kidney impairment[51] as discussed previously (see the third overarching principle).

Unlike the 2006 guideline in which the group of experts recommended starting ULT only for patients with certain severe clinical features, including recurrent acute attacks and tophi (item 7), the current task force recommends possible initiation of ULT close to the first presentation (ie, in most cases, close to the first attack). Indeed, the task force felt that delaying initiation of ULT until the second or third attack would expose patients to a higher crystal load, for difficulties in dissolution and to longstanding hyperuricaemia, which may be deleterious for the cardiovascular system and kidney.[51 56 107–110] Therefore, the recommendation to initiate ULT earlier was mainly based on expert opinion but also took into account studies that suggest a cardiovascular[111 112] and renal benefit[113–116] from xanthine oxidase inhibitors (XOI). XO inhibition improved exercise capacity in patients with chronic stable angina in a randomised cross-over trial.[117] Epidemiological studies suggested that allopurinol might decrease morbidity and mortality in patients with congestive heart failure and a history of gout,[118 119] a benefit not confirmed in a recent randomised trial of patients with heart failure and hyperuricaemia without gout.[120] In addition, pharmaco-epidemiological studies report that allopurinol use is associated with an approximately 20% reduction in myocardial infarction risk.[121 122] However, the task force acknowledged that additional well-conducted trials are warranted in this field, as recent studies yielded conflicting results.[123 124]

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Item 5 also underlines the need to start ULT early, particularly in patients with comorbidities and/or SUA level >8 mg/dL. Encouragement to treat patients with high SUA level earlier is based on studies showing an association of high uricaemia with increased flare frequency.[125–127] Similarly, early treatment in patients with comorbidities is supported by a study of a large cohort of gout patients finding hypertension, ischaemic heart disease and CKD all associated with increased risk of recurrence of flare.[128] Young age at gout onset is also a marker of gout severity[129] and should also prompt earlier treatment. This recommendation underlines again the importance of providing full information and involving the patient in the decision-making process, to ensure adherence to ULT and optimal patient-centred outcomes.

Finally, the task force did not give specific guidance on whether urate-lowering drugs should be initiated during a flare or whether a traditional 2 weeks delay from flare termination should be observed. Two small trials have suggested that allopurinol initiation during an acute gout attack did not prolong the duration of flares nor worsen its severity as compared with delayed initiation.[130 131] However, the task force considered that the low number of patients (n=51 and n=31, respectively) in these trials precluded any firm conclusions and that data obtained with allopurinol 200–300 mg could not be generalised to more potent urate-lowering drugs, such as febuxostat or a combination of XOI and an uricosuric.

6. *For patients on ULT, SUA level should be monitored and maintained to <6 mg/dL (360 µmol/L). A lower SUA target (<5 mg/dL; 300 µmol/L) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout. SUA level <3 mg/dL is not recommended in the long term.*

As in 2006 (item 8), the task force recommends a treat-to-target strategy for every patient with gout, to maintain the SUA level <6 mg/dL, which is below the saturation point for MSU[132] to dissolve all crystal deposits.[133] Because the velocity of crystal dissolution depends on the SUA level,[134 135] the task force also recommends reducing the SUA level to <5 mg/dL for severe gout reflecting high crystal load until total crystal dissolution has occurred. The task force also agreed that once dissolution of crystals is achieved, SUA level could be maintained <6 mg/dL by a reduction in the dose of ULT to avoid new formation of urate crystals.

Some studies, but not all,[136–138] have suggested that uric acid might protect against various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease or amyotrophic lateral sclerosis.[139–142] Given these data and the availability of ULT that has the potency to greatly decrease SUA levels, the task force does not recommend lowering continuously the SUA level to <3 mg/dL in the long term that is, for several years.

7. *All ULTs should be started at a low dose and then titrated upward until the SUA target is reached. SUA <6 mg/dL (360 µmol/L) should be maintained lifelong.*

The task force recommends upward titration of ULT in every patient when feasible. This approach, mentioned in 2006 (item 9), might result in fewer episodes of acute flares during treatment initiation[28] and therefore improved adherence to ULT, which is low according to several studies.[27 143 144] Following complete dissolution of MSU crystals, the SUA level should be maintained at <6 mg/dL lifelong. Indeed, a study showed that about 40% of successfully treated patients show recurrence of flare 5 years after withdrawal of ULT.[145] Therefore, determining SUA level on a regular basis is a key aspect of treatment.

8. *In patients with normal kidney function, allopurinol is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricaemic target. If the SUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric, or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated.*

As in 2006 (item 9), the task force recommends the use of allopurinol as first-line therapy in patients with normal kidney function. This recommendation takes into account the efficacy, low cost and safety of this drug. Since 2006, two RCTs have confirmed the superior urate-lowering efficacy of allopurinol (300 mg/day) over placebo.[97 130] Medico-economic studies of ULT reported that a dose-escalation strategy with allopurinol as first-line therapy was cost-effective.[146 147] Allopurinol should be started at a low dose (100 mg/day) to reduce early gout flare[28] and because high starting doses might increase the risk of serious cutaneous adverse reactions (SCARs).[15] The most commonly used allopurinol dose of 300 mg/day does not achieve the SUA target of 6 mg/dL (360 µmol/L) in about 30%–50% of patients with normal kidney function.[28 148 149] For those patients, the task force recommends a dose-escalation strategy to increase the dose in order to reach the predefined uricaemia target. Treatment with allopurinol up to 600–800 mg/day had a 75%–80% success rate of achieving SUA levels of <6 mg/dL (360 µmol/L).[28 150]

Febuxostat is a potent non-purine selective XOI approved at daily doses of 80 and 120 mg in Europe. It is metabolised in the liver and renal excretion is not a major route of elimination, which allows for its use in patients with mild-to-moderate kidney failure. A short-term phase II trial[151] and three large RCTs (see online supplementary material) showed superior urate-lowering efficacy with febuxostat (80 or 120 mg) as compared with the commonly used fixed daily dose of 300 mg allopurinol.[97 98 149] Cutaneous reactions have been described in pivotal trials with febuxostat.[97 149] Despite case reports of SCARs in patients receiving febuxostat,[152 153] recent data do not support any cross-reactivity between the two drugs.[153 154] Therefore, the task force considered that a history of allergic reaction to allopurinol was not a contraindication to febuxostat, but underlined the need to carefully follow these patients.

Uricosurics are recommended, where available, alone or in combination with allopurinol in patients without proper control with allopurinol alone. Benzbromarone (50–200 mg/day) is a more potent uricosuric as compared with probenecid (1–2 g/day).[155] In an RCT of patients without proper control with allopurinol, 300 mg/daily, 92% and 65% of patients reached a SUA target of 300 µmol/L (5 mg/dL) when switched to benzbromarone, 200 mg, or probenecid, 2 g daily, respectively.[148] Finally, the recommendation for combination therapy with allopurinol and a uricosuric, not mentioned in 2006, is based on uncontrolled trials that have suggested that probenecid-allopurinol[156–158] or benzbromarone-allopurinol[135] was more effective than allopurinol alone. Furthermore, emerging uricosuric, such as lesinurad,[159] has shown promising results in a phase II trial when combined with allopurinol.[160]

9. *In patients with renal impairment, the allopurinol maximum dosage should be adjusted to creatinine clearance. If the SUA target cannot be achieved at this dose, the patient should be switched to febuxostat or given benzbromarone with or without allopurinol, except in patients with eGFR <30 mL/min.*

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This item retained the 2006 recommendation (item 9) to adjust the allopurinol dosage according to the creatinine clearance. The greatest concern with the use of allopurinol in patients with renal failure is the development of SCARs, which includes drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis. Since 2006, several studies have further explored allopurinol-induced SCARs. Allopurinol was found to be the most common drug associated with SJS or toxic epidermal necrolysis in Europe.[161] Allopurinol-induced SCARs are rare, the incidence rate being about 0.7/1000 patient-years in allopurinol initiators in the USA,[162] but the mortality rate is high (25%–30%).[163–165]

Renal failure has been associated with an increased risk of SCARs and poor outcome.[163 164] Decreased renal function results in decreased clearance and higher serum levels of oxypurinol,[164 166] which could induce a cytotoxic T-cell response and trigger hypersensitivity reactions in SCARs.[167] In some studies, dose escalation of allopurinol above the limit allowed by creatinine clearance did not result in SCARs,[14 168] but given the very low incidence of SCARs and the limited number of patients involved in these studies, the task force considered that they probably lacked power to detect a potential association.

Therefore, given the extreme severity of SCARs and the possibility of therapeutic alternatives such as febuxostat, the task force retained the conservative approach to adjust the maximum dose of allopurinol to the creatinine clearance[169] in patients with renal impairment, as required by most regulatory agencies. Because the dose recommendations in renal disease may slightly differ across countries, the task force recommends to follow the local Summary of Product Characteristics.

Febuxostat has been found more effective in patients with CKD than allopurinol given at doses adjusted to creatinine clearance[149 170] and therefore can be used in these patients. Finally, benzbromarone is not recommended for use in patients with eGFR <30 mL/min, but can be used in patients with moderate renal impairment[171 172] because it is predominately metabolised by the liver.

10. *In patients with crystal-proven severe debilitating chronic tophaceous gout and poor quality of life, in whom the SUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated.*

Since the last EULAR recommendation, pegloticase has emerged as a powerful ULT for refractory gout. Pegloticase is a pegylated uricase, produced by a genetically modified strain of *Escherichia coli* that catalyses the oxidation of uric acid into allantoin, a more soluble end product.[173] Its efficacy has been assessed in two replicate 6-month, randomised, double-blind, placebo-controlled, phase III trials.[99 100] In this study, the percentage of responders (SUA level <6 mg/dL) was 42%, on average, in patients who received pegloticase, 8 mg, every 2 weeks and 0% in the placebo group. Allergic reactions, possibly related to the occurrence of antibody against pegloticase,[174] were observed in about 25% of patients who received pegloticase biweekly. Given the safety profile of pegloticase and the demonstration of its efficacy in patients with refractory gout, the task force recommends its use in patients with clinically severe crystal-proven gout that cannot be properly treated with conventional ULT, including a combination of an XOI and a uricosuric agent. There was no firm agreement with regards to the duration of treatment with pegloticase. However, there was a consensus to consider a switch, if feasible, toward an oral ULT once all tophi had disappeared.

11. *When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible; for hypertension, consider losartan or calcium channel blockers; for hyperlipidaemia, consider a statin or fenofibrate.*

This recommendation is similar to the 12th 2006 recommendation. However, in addition to losartan, the task force now recommends consideration of calcium blockers in patients with gout. This recommendation is supported by a large epidemiological study finding relative risks of incident gout associated with the current use of calcium channel blockers and losartan of 0.87 (95% CI 0.82 to 0.93) and 0.81 (95% CI 0.70 to 0.94), respectively.[175] Finally, the uricosuric property of fenofibrate[176 177] and statins has been further documented.[178 179]

DISCUSSION

These updated EULAR recommendations aim to provide physicians—rheumatologists, GPs and others—with the best pragmatic strategies to manage hyperuricaemia and flare in patients with gout (figures 1 and 2).

As first-line care providers, GPs have a predominant role in gout treatment. Likewise, the involvement of patients in the management of chronic diseases is crucial. Therefore, in contrast to 2006, the current task force included two GPs and two patients to broaden the involvement of stakeholders involved in the disease. As mentioned previously, gout is mainly managed by GPs, and the task force recognises that we lack trials conducted in primary care; most of the RCTs analysed in this paper were conducted in tertiary care. Overall, this set of recommendations was well graded by external GPs and rheumatologists (see online supplementary material).

Since 2006, the perception of gout has changed. The increase in prevalence of gout in developed countries,[1–3 180] the severity of the arthritis itself,[6] and the increasing evidence for an association between gout with cardiovascular events, kidney failure and mortality have heightened the realisation that gout should never be neglected and should be treated properly.[6] Furthermore, since 2006, the treatment armamentarium has greatly expanded, with the approval of both febuxostat and pegloticase, the demonstration of the efficacy of IL-1 blockers to treat flare and the emergence of novel ULTs.[11 12 181] As expected, the task force modified all the previous 2006 recommendation items to incorporate all these recent developments and altered perspectives that have resulted from recent research evidence.

As compared with 2006, the key differences in terms of the therapeutic strategy for the management of hyperuricaemia are the recommendations to titrate and initiate ULT very early in the course of the disease, to combine an XOI and a uricosuric, and for patients with severe gout to reach a target SUA level of 5 mg/dL (300 μmol/L) to hasten crystal dissolution. The task force was convinced that treatment of hyperuricaemia should be target-oriented and initiated without delay to avoid a further longstanding period of silent urate deposits.[182–184] In addition, a 'start low, go slow' approach is recommended, because it probably results in fewer episodes of acute gout during treatment initiation and therefore might improve ULT adherence.

The task force was aware that not all ULTs mentioned in this paper, especially the uricosurics, are readily available in all European countries. However, it felt that these older drugs, in the absence of available new ULTs, could benefit some patients without adequate control with allopurinol or febuxostat alone. Of note, the recommendation to combine benzbromarone or

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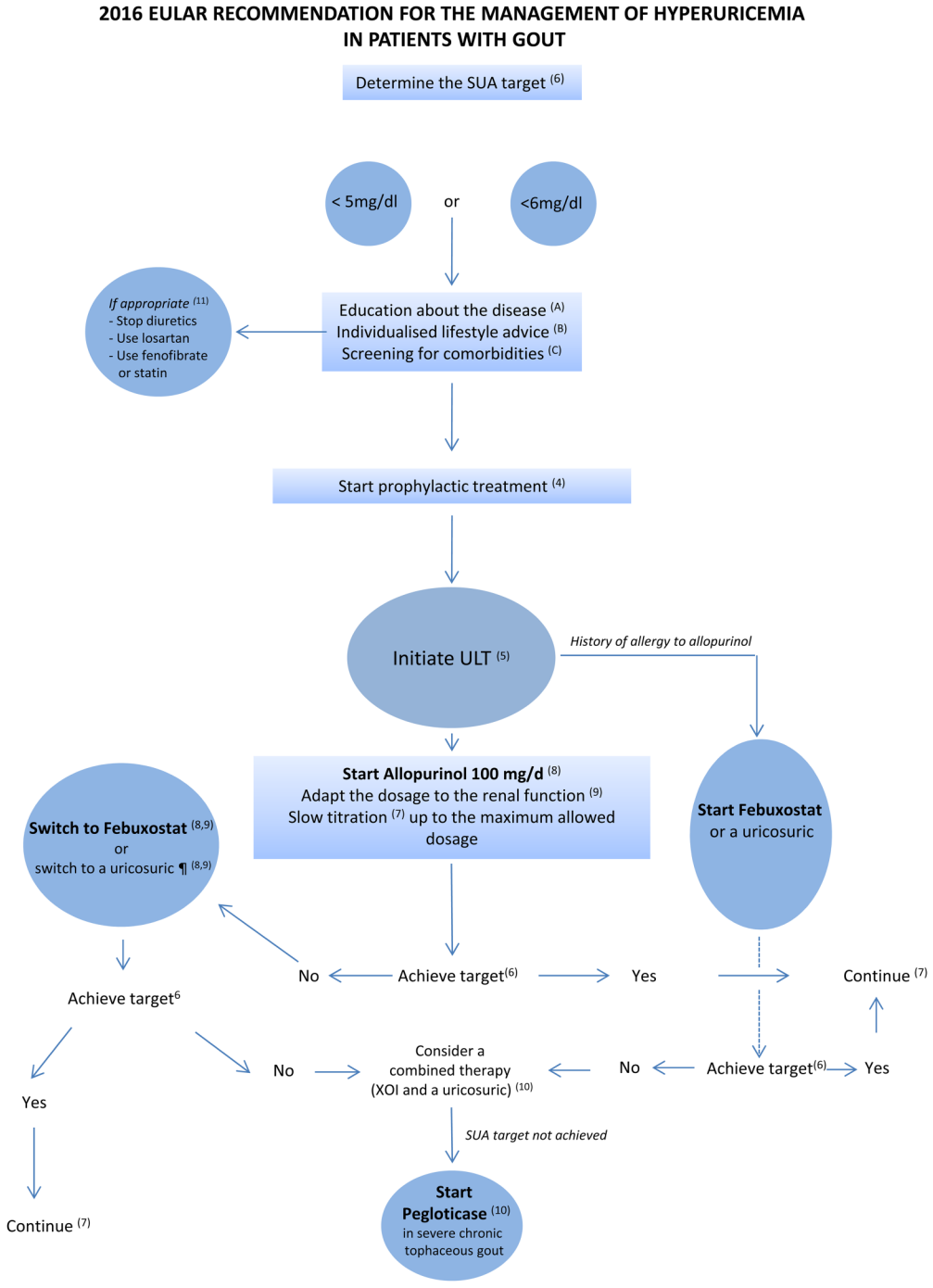
2016 EULAR RECOMMENDATION FOR THE MANAGEMENT OF HYPERURICEMIA IN PATIENTS WITH GOUT
Determine the SUA target (6)
< 5mg/dl
or
<6mg/dl
If appropriate (11)
- Stop diuretics
- Use losartan
- Use fenofibrate or statin
Education about the disease (A)
Individualised lifestyle advice (B)
Screening for comorbidities (C)
Start prophylactic treatment (4)
Initiate ULT (5)
History of allergy to allopurinol
Start Allopurinol 100 mg/d (8)
Adapt the dosage to the renal function (9)
Slow titration (7) up to the maximum allowed dosage
Switch to Febuxostat (8,9) or switch to a uricosuric ¶ (8,9)
Start Febuxostat or a uricosuric
No
Achieve target(6)
Yes
Continue (7)
Achieve target6
No
Consider a combined therapy (XOI and a uricosuric) (10)
No
Achieve target(6)
Yes
Yes
SUA target not achieved
Continue (7)
Start Pegloticase (10) in severe chronic tophaceous gout

Figure 2 Management of hyperuricaemia in patients with gout according to the European League Against Rheumatism recommendations. Letters and numbers in parentheses refer to the items of the recommendations presented in table 1. SUA, serum uric acid; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor. ¶At this stage, combined allopurinol and a uricosuric is also recommended.

probenecid with an XOI is a novel strategy that should help physicians manage severe gout that is not readily controlled by single agents and not eligible for pegloticase. This recommendation was not strictly evidence-based and relied more on expert opinion and on recent data from phase II trials showing the potency to combine allopurinol or febuxostat with lesinurad, a novel uricosuric targeting URAT1.[11 160]

These revised EULAR recommendations differ in some aspects from the 2012 American College of Rheumatology (ACR) guidelines.[185 186] For instance, ACR recommends allopurinol or febuxostat as first-line therapy, whereas EULAR recommends allopurinol first and then febuxostat with failure to achieve the predetermined SUA target. As indicated previously, this recommendation was not supported by efficacy data, but rather took into account the cost and effectiveness of both drugs at their optimal dosage as well as regulatory rules endorsed in several European countries. Importantly, unlike the ACR, the EULAR recommends adjusting the dosage of allopurinol to the creatinine clearance in patients with renal failure, owing to an increased risk of SCARs in those patients,[164] and febuxostat as an alternative if the SUA target is not reached.

The ACR also recommended that ULT could be started during an acute attack[185] if anti-inflammatory treatment had been introduced, a strategy not recommended in the present paper.

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These recommendations also did not mention systematic HLA-B*5801 screening before the initiation of allopurinol. This haplotype is the strongest risk factor for allopurinol-induced SCARs,[187] and oxypurinol, the serum levels of which are increased in patients with renal failure,[164] can preferentially bind to the peptide binding groove of HLA-B*58:01 and dose-dependently activate T cells.[188 189] The association between carriage of this allele and increased risk of SCARs has been mainly observed in certain ethnic populations, including Han Chinese, Thai and Korean patients, showing high allele frequency.[187] By contrast, in Europe, where the allele frequency is much lower, allopurinol-induced SCARs have been reported also in the absence of this haplotype.[190] Although studies conducted in Asia found that screening for HLA-B*58:01 was cost-effective[191 192] and reduced the incidence of allopurinol-induced SCARs,[159] the task force felt that we lack sufficient data to provide firm recommendations for cost-effective screening in populations with low allele frequency, such as Europe. Therefore, screening for this haplotype before initiating allopurinol is left to the discretion of the attending physician, who should however be aware of the genetic risk of severe allergic reaction conferred by HLA-B*58.01 carriage.

Recommendations for the treatment of flares have also markedly evolved since 2006 in that use of colchicine should be tailored according to current medications and comorbidities, oral corticosteroids can be offered and a combination of anti-inflammatory agents is now recommended depending on the severity of flares. Items related to colchicine, NSAIDs and oral corticosteroids are now predominantly evidence-based, whereas those related to combined therapy and intra-articular corticosteroid injections rely on expert and patient opinion, which highlights the need for further trials. The other main novelty for treatment of flares is the recommendation for IL-1 blockade in patients with frequent, poorly controlled flares. Given the price and putative infection risk associated with IL-1 blockers, the task force recommends their use in patients with contraindications to colchicine, NSAIDs and corticosteroids. Finally, the need to educate patients and to promote a 'pill-in-the-pocket' approach is highlighted to provide rapid treatment of flares, because the task force is convinced that patients must play a key role and be fully involved in the management of their disease.

These novel EULAR recommendations will undoubtedly require updating over the next few years. Indeed, we anticipate that new data on existing drugs or emerging drugs, in particular novel uricosurics, will be available soon. In addition, studies of therapeutic strategies are likely to emerge. The task force sincerely hopes that these pragmatic recommendations will improve the current quality of gout care.

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2018 update of the EULAR recommendations for the management of hand osteoarthritis

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ABSTRACT

Since publication of the European League Against Rheumatism (EULAR) recommendations for management of hand osteoarthritis (OA) in 2007 new evidence has emerged. The aim was to update these recommendations. EULAR standardised operating procedures were followed. A systematic literature review was performed, collecting the evidence regarding all non-pharmacological, pharmacological and surgical treatment options for hand OA published to date. Based on the evidence and expert opinion from an international task force of 19 physicians, healthcare professionals and patients from 10 European countries formulated overarching principles and recommendations. Level of evidence, grade of recommendation and level of agreement were allocated to each statement. Five overarching principles and 10 recommendations were agreed on. The overarching principles cover treatment goals, information provision, individualisation of treatment, shared decision-making and the need to consider multidisciplinary and multimodal (non-pharmacological, pharmacological, surgical) treatment approaches. Recommendations 1–3 cover different non-pharmacological treatment options (education, assistive devices, exercises and orthoses). Recommendations 4–8 describe the role of different pharmacological treatments, including topical treatments (preferred over systemic treatments, topical non-steroidal anti-inflammatory drugs (NSAIDs) being first-line choice), oral analgesics (particularly NSAIDs to be considered for symptom relief for a limited duration), chondroitin sulfate (for symptom relief), intra-articular glucocorticoids (generally not recommended, consider for painful interphalangeal OA) and conventional/biological disease-modifying antirheumatic drugs (discouraged). Considerations for surgery are described in recommendation 9. The last recommendation relates to follow-up. The presented EULAR recommendations provide up-to-date guidance on the management of hand OA, based on expert opinion and research evidence.

INTRODUCTION

Hand osteoarthritis (OA) is a common musculoskeletal disease, with prevalence rising steeply with increasing age.[1–3] The disease is associated with hand pain, stiffness, functional limitation, decreased grip strength and reduced quality of life.[4–6] Clinical hallmarks of the disease include bony enlargement and deformities of the hand joints, at times accompanied by soft tissue swelling.[7] Hand OA has a variable disease course.[8] The first European League Against Rheumatism (EULAR) recommendations for the management of hand OA were published in 2007.[9] The American College of Rheumatology (ACR) published management recommendations for hand, hip and knee OA in 2012, including evidence available to the end of 2010, and other societies, including an expert group of occupational therapists and the Italian Society for Rheumatology, formulated treatment recommendations in 2011 and 2013, respectively.[10–12]

For a long time, hand OA was a 'forgotten disease', resulting in a paucity of clinical trials to guide recommendations, and therefore many of the propositions of previous recommendations were based mainly on expert opinion.[13] However, in recent years, hand OA has attracted more attention, and new data have become available on several pharmacological and non-pharmacological treatments, including but not limited to: self-management, application of thumb base orthoses, topical non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, various intra-articular therapies and treatment with conventional synthetic and biological disease-modifying antirheumatic drugs (cs/bDMARDs), for example, hydroxychloroquine and tumour necrosis factor (TNF) inhibitors.

These more recent data have given new insights into treatment options. It was therefore timely to update the 2007 management recommendations. In this paper, we present the 2018 update of the EULAR recommendations for the management of hand OA.

METHODS

The development of the update was performed according to the 2014 EULAR Standard Operating Procedure (SOP).[14] As prescribed by the SOP, the process set out in Appraisal of Guidelines for Research & Evaluation II (AGREE II) was followed.[15] The convenor (MK), methodologist (LC) and fellow (FK) defined research questions for the systematic literature review (SLR) and prepared a 1-day task force meeting. The task force further comprised 10 rheumatologists, 1 plastic surgeon (MR), 3 healthcare professionals in the field of physiotherapy and occupational therapy (KD, IK, TS) and 2 patient research partners (EG, WS). Two task force members were Emerging EUlar NETwork members (IKH, FK). The task force represented 10 countries across Europe.

Under guidance of the methodologist, the fellow performed an SLR on the efficacy and safety of all

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non-pharmacological, pharmacological and surgical therapies available for hand OA. Although published separately, the SLR[16] and the current updated management recommendations are complementary and should be considered together.

To explore current clinical practice in hand OA treatment and which topics healthcare professionals and patients felt should be covered in the update of the recommendations, members of the task force completed an online survey prior to the 1 day meeting.

Using the previous recommendations as a basis, together with the data obtained from the survey and the SLR, the convenor, methodologist and fellow prepared a proposal for wording for the update of the recommendations.

The results of the survey and the SLR were sent to the task force members in advance of a 1 day meeting where they were again presented. Through group discussion, overarching principles were formulated and the recommendations were updated. For every proposed overarching principle and recommendation, the results from the survey, evidence from the SLR and a proposed formulation were presented. Following discussion and rewording of the statement, voting was undertaken. A 75% majority was required to approve the statement. In case of disagreement, discussion was resumed and changes to the statement were made. The second voting round required a 67% majority, and if the formulation remained unagreed, an additional round of discussion followed. The third voting round required only 50% support for approval of the statement. The wording of the statements was considered final after the 1 day meeting.

After the meeting, the level of evidence (LoE) and grade of recommendation (GoR) were added to each recommendation, derived from the evidence from the SLR and according to the Oxford Centre for Evidence-Based Medicine standards.[17] Finally, the overarching principles and recommendations (including LoE and GoR, and rationale for each statement based on the survey data, evidence from the SLR and discussion during the 1 day meeting) were sent to all task force members, who were asked to add their level of agreement (LoA) to each of the statements. The vote for the LoA was carried out anonymously on a numerical rating scale of 0–10 (0: do not agree at all, 10: fully agree). The mean and SD were calculated.

The final manuscript was reviewed, revised and approved by all task force members, followed by a final review by the EULAR Executive Committee.

RESULTS

Overarching principles

Overarching principles were not stated in the 2007 recommendations and were a new inclusion in the 2018 update. Overarching principles are generic statements, serving as the basis for management of patients with hand OA. Some of the 2007 recommendations were included in the 2018 update in the form of an overarching principle. The LoA of each overarching principle is presented in table 1.

The primary goal of managing hand OA is to control symptoms, such as pain and stiffness, and to optimise hand function, in order to maximise activity, participation and quality of life

Management should aim to achieve the best possible activity performance, participation and quality of life. Studies have shown that patients with hand OA have a decreased health-related

Table 1 2018 Update of the EULAR recommendations for the management of hand OA

		LoE*	GoR†	LoA (0–10)
Overarching principles				
A.	The primary goal of managing hand OA is to control symptoms, such as pain and stiffness, and to optimise hand function, in order to maximise activity, participation and quality of life.			9.7 (0.7)
B.	All patients should be offered information on the nature and course of the disease, as well as education on self-management principles and treatment options.			9.8 (0.8)
C.	Management of hand OA should be individualised taking into account its localisation and severity, as well as comorbidities.			9.9 (0.2)
D.	Management of hand OA should be based on a shared decision between the patient and the health professional.			9.6 (1.1)
E.	Optimal management of hand OA usually requires a multidisciplinary approach. In addition to non-pharmacological modalities, pharmacological options and surgery should be considered.			9.3 (1.2)
Recommendations				
1.	Education and training in ergonomic principles, pacing of activity and use of assistive devices should be offered to every patient.	1b	A	9.3 (1.1)
2.	Exercises to improve function and muscle strength, as well as to reduce pain, should be considered for every patient.	1a	A	9.1 (1.6)
3.	Orthoses should be considered for symptom relief in patients with thumb base OA. Long-term use is advocated.	1b	A	9.3 (1.0)
4.	Topical treatments are preferred over systemic treatments because of safety reasons. Topical NSAIDs are the first pharmacological topical treatment of choice.	1b	A	8.6 (1.8)
5.	Oral analgesics, particularly NSAIDs, should be considered for a limited duration for relief of symptoms.	1a	A	9.4 (0.9)
6.	Chondroitin sulfate may be used in patients with hand OA for pain relief and improvement in functioning.	1b	A	7.3 (2.7)
7.	Intra-articular injections of glucocorticoids should not generally be used in patients with hand OA‡, but may be considered in patients with painful interphalangeal joints§.	1a‡–1b§	A	7.9 (2.4)
8.	Patients with hand OA should not be treated with conventional or biological disease-modifying antirheumatic drugs	1a	A	8.8 (1.8)
9.	Surgery should be considered for patients with structural abnormalities when other treatment modalities have not been sufficiently effective in relieving pain. Trapeziectomy should be considered in patients with thumb base OA and arthrodesis or arthroplasty in patients with interphalangeal OA.	5	D	9.4 (1.4)
10.	Long-term follow-up of patients with hand OA should be adapted to the patient's individual needs.	5	D	9.5 (1.7)

*1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT; eg,<80% follow-up); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.[17]

†A: based on consistent level 1 evidence; B: based on consistent level 2 or 3 evidence or extrapolations from level 1 evidence; C: based on level 4 evidence or extrapolations from level 2 or 3 evidence; D: based on level 5 evidence or on troublingly inconsistent or inconclusive studies of any level.[17]

EULAR, European League Against Rheumatism; GoR, grade of recommendation; LoA, level of agreement; LoE, level of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; RCT, randomised clinical trial.

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quality of life.[18] Symptoms such as pain, stiffness and decreased hand function are hallmarks of the disease, and contribute to altered quality of life.[6 19] This overarching principle was based on the International Classification of Functioning, Disability and Health framework.[20] The wording 'optimise' and 'maximise' were chosen to reflect that management of hand OA should be more ambitious than merely aiming for a patient-acceptable symptom state.

All patients should be offered information on the nature and course of the disease, as well as education on self-management principles and treatment options

Education is considered a core treatment in the management of patients with hand OA, and should be offered to all patients. This overarching principle is an additional, more generic statement on education, besides the first recommendation concerning specific education and training. In patients with chronic complaints returning for follow-up, information and education provision should be an ongoing process involving reinforcement and expansion. Explicit evidence supporting the efficacy and content of provision of information and education in hand OA is lacking. Trained health professionals other than the physician can play an important role in the provision of information and education.

Management of hand OA should be individualised taking into account its localisation and severity, as well as comorbidities

This overarching principle was modified from the 2007 recommendation about individualisation of treatment. In the premeeting survey, >75% of health professionals indicated that patient characteristics that are considered important include: age, type of complaint (eg, pain or disability), mechanical factors, patient's wishes and expectations, presence of inflammation, severity of structural damage and presence of erosions. In the survey, most health professionals also supported different treatment approaches according to disease location (especially thumb base OA) or OA subset (especially erosive or 'inflammatory' OA). The 2007 recommendation included consideration of many of these individual factors. Yet although many of these factors are known to be determinants of worse outcome (eg, presence of inflammation is known to be associated with disease progression[21–23]), evidence of effect modification is lacking for most of these factors.[24] Moreover, it is unknown whether treatment of modifiable factors will in turn change disease outcomes (eg, there is no evidence that treatment of inflammation reduces disease progression). OA localisation (most importantly finger vs thumb base OA), OA severity and presence of comorbidities were thought to be the only aspects that may currently influence treatment decisions. This is also reflected in the recommendations. 'Severity' can encompass several features, including a high number of hand joints with OA, one or two severely affected joints or acute joint inflammation due to OA. The patient's wishes and expectations were not mentioned separately in this overarching principle, since this concept is incorporated in the overarching principle concerning shared decision-making.

Management of hand OA should be based on a shared decision between the patient and the health professional

Shared decision-making, an approach to healthcare in which health professionals and patients mutually share information to reach consensus about the preferred management strategy, should be the basis of management in hand OA.[25] This overarching principle implies that not only the best available evidence, but also the patients' wishes and expectations are important to be considered when making decisions on managing the disease. Achieving shared decision-making depends on building and maintaining a good relationship between patient and health professional, and sharing the best evidence, in order to be able to make an informed decision. It pertains to all stages of management, including, for example, setting a treatment goal, choosing the best strategy to achieve it or considering other strategies when the treatment goal is not reached.

Optimal management of hand OA usually requires a multidisciplinary approach. In addition to non-pharmacological modalities, pharmacological options and surgery should be considered

Hand OA is both a heterogeneous disease, leading to a variety of signs and symptoms, and a chronic disease. Over the course of the disease, patients with hand OA therefore often require multidisciplinary care. Health professionals involved in care for patients with hand OA, may include, for example, the general practitioner, rheumatologist, occupational or physical therapist, orthopaedic or plastic surgeon and the rehabilitation specialist. Which care is delivered by each health professional differs by country, depending for example on local preferences or customs and social security systems. In some clinics, structured multidisciplinary care programmes or integrated care pathways are provided. However, it is unclear whether such programmes providing a structured combination of different non-pharmacological therapies are efficacious. For example, no consistent beneficial effect of combination programmes including education, joint protection and exercises over education alone has been determined.[26–28]

The second part of this overarching principle, that different treatment modalities should be considered, was modified from the first 2007 recommendation, and initially discussed as a separate overarching principle (LoA: 100%). Later, the concept 'multidisciplinary care' was added, since it was recognised that different modalities may be provided by different health professionals. By modifying the 2007 recommendation, this overarching principle now also reflects that the first step in hand OA management should focus on non-pharmacological therapies, which may be complemented by pharmacological and/or surgical options, although not necessarily for all patients with hand OA, depending on the level of symptoms.

Recommendations

In total, 10 recommendations were formulated (table 1). Table 1 also presents the LoE, GoR and LoA for each recommendation. Many of the 2007 recommendations were modified because new evidence has emerged since the previous SLR, and were formulated as recommendations rather than 'statements' reflecting the state of the evidence and/or expert opinion. Two recommendations are new (#8, #10), one recommendation was split into two (old #3 into new #1 and #2), two recommendations were combined into one (old #7 and #8 into new #5) and one recommendation was deleted (old #4). The recommendation that was deleted concerned the use of heat and ultrasound, which was based on expert opinion and extrapolation from hip or knee OA studies.

Education and training in ergonomic principles, pacing of activity and use of assistive devices should be offered to every patient

Education and training in ergonomic principles and pacing of activity, formerly included in the recommendations under the

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term 'joint protection', is an important aspect of management, and has been shown to be efficacious in one study.[26] The term 'joint protection', although still often used, was viewed by the task force as an outdated concept, implying that one should protect the joints and refrain from using them. It was thus replaced by a more explicit statement of what the education and training should consist of. The use of assistive devices is an important and commonly used strategy to improve patient's self-management, and shown to be efficacious.[29 30] No evidence is available that intensive programmes delivering this care are more effective or cost-effective than more simple strategies.[31] This care can be delivered by any health professional specialised in these interventions (eg, an occupational or physical therapist or a trained nurse).

Exercises to improve function and muscle strength, as well as to reduce pain, should be considered for every patient

Although exercise was endorsed in the 2007 recommendations, no supporting evidence was available at that time. Since then, multiple trials (n=7) have been performed, and their results were summarised in a Cochrane review.[32] It was shown that hand exercises have small beneficial effects on self-reported pain and function, joint stiffness and grip strength, while resulting in few and non-severe adverse effects. However, the interventions studied were heterogeneous, varying from home-based exercises after a single instruction session to multiple supervised sessions per week for several weeks, and also the frequency of exercising, number of repetitions per exercise and type of exercises (eg, strengthening or stretching) were variable. Furthermore, the review authors debated whether the effects that were found constituted a clinically relevant improvement, and the beneficial effects were not sustained when patients stopped exercising. Exercises should aim at improving joint mobility, muscle strength and thumb base stability. Exercise regimens aimed at the first carpometacarpal (CMC-1) joint differ from those for interphalangeal joints.

Orthoses should be considered for symptom relief in patients with thumb base OA. Long-term use is advocated

Since the 2007 recommendations many orthosis trials have been performed, of which five compared orthoses to usual care or a non-pharmacological intervention.[33–37] These trials provide evidence for beneficial effects of a thumb base orthosis, especially on pain and to a lesser extent on function, but not on grip strength, when used for a prolonged period (at least 3 months). No improvements were evident when used for shorter periods. Long-term use is thus advocated. The 2007 recommendations advised the use of orthoses to 'prevent/correct lateral angulation and flexion deformity' in patients with thumb base OA, yet no evidence to date supports an effect of orthoses on angulation or deformity, and therefore the statement was reworded.

No straightforward advice can be given for the type of orthosis (short or long, custom-made or prefabricated, neoprene, thermoplast or other material) or instructions for use (eg, during activities of daily living, at night, constantly), as studies are heterogeneous and no consistent benefit of one type of orthosis over the other could be identified. Trials showing a long-term beneficial effect of orthosis use investigated a custom-made thermoplast long orthosis to be worn during activities of daily living,[35] and a custom-made neoprene long orthosis to be worn at night.[37]

It is important to pay attention to prescribing a well-fitted orthosis, preferably custom-made by a specialised health professional. This will likely improve patients' compliance and increase long-term use.

Most trials were performed in patients with thumb base OA, and only one trial investigated night-time distal interphalangeal joint (DIP) orthoses, which did not prove to be efficacious, and is therefore not specifically recommended.[38]

Topical treatments are preferred over systemic treatments because of safety reasons. Topical NSAIDs are the first pharmacological topical treatment of choice

Topical NSAIDs are recommended as a first-line pharmacological treatment, due to their favourable safety profile compared with oral analgesics and beneficial effects on pain and function.[39–41] Topical diclofenac gel showed small improvements in pain and function after 8 weeks compared with placebo in one high-quality study.[41] Moreover, topical NSAIDs can show similar pain relief as oral NSAIDs.[39 40] Pooled safety data from randomised clinical trials comparing topical diclofenac gel with placebo in patients with hand and knee OA also showed similar low rates of adverse effects in subgroups of low-risk versus high-risk patients (ie, age ≥65 years, and with comorbid hypertension, type 2 diabetes or cerebrovascular or cardiovascular disease).[42] When a large number of joints are affected, systemic pharmacological treatment may be preferred. At present, no data are available on long-term effects of topical NSAIDs.[43]

Capsaicin is another topical treatment, which is however known to be associated with frequent local adverse effects (burning and stinging sensation), and therefore success of blinding of the (positive) placebo-controlled trial investigating its efficacy is questionable.[44]

Topical application of heat was regarded by the task force as a self-management strategy that patients can apply at home, with weak and conflicting evidence for a possible beneficial effect.[45–47] It was therefore not included as a separate recommendation in this update. Cold packs, in case of inflammation during an OA flare, may also give symptomatic relief, though studies in hand OA have not been performed, and a single knee OA study comparing hot and cold application with usual care found no between-group differences.[48]

Oral analgesics, particularly NSAIDs, should be considered for a limited duration for relief of symptoms

This recommendation is a combination of the 2007 recommendations concerning paracetamol and oral NSAIDs.

Oral NSAIDs effectively improved pain and function after 2–4 weeks in three high-quality studies.[49–51] However, adverse effects are well-known, especially in the elderly. No new evidence was identified compared with the 2007 recommendations. The advice to prescribe NSAIDs at the lowest effective dose, for a limited duration (preferably on-demand), with attention for the risk-benefit ratio, especially in patients at high risk of gastrointestinal, cardiovascular or renal adverse effects, remains unchanged.

Paracetamol is prescribed by many health professionals, and also in the premeeting survey the vast majority of health professionals indicated that they prescribed paracetamol to their patients with hand OA. Patients' experience with paracetamol is known to be variable. It has generally been regarded as a safe treatment option, although lately its risk-benefit profile has been a topic of debate, even leading to controversy about including it in the National Institute for Health and Care Excellence (NICE) guidelines on OA.[52] Three small trials, two only published as conference abstracts, have studied paracetamol (1000–3900 mg

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daily) in hand OA.[53–55] In these trials, paracetamol was not superior over placebo or an active comparator. Two large meta-analyses of trials in patients with knee and hip OA found small effects on pain, with doubtful clinical significance.[56 57] Evidence from these trials showed that paracetamol was associated with an increased risk of liver test abnormalities, although the clinical relevance of this finding is unknown, but not with increased risk of any other safety parameter.[57] A narrative review of long-term observational studies in the general adult population found a dose-response increased risk of mortality (n=2 trials), cardiovascular (n=4), gastrointestinal (n=1) and renal adverse effects (n=4). This should, however, be interpreted with caution, as these observational studies were associated with a large risk of bias (most importantly confounding by indication) and imprecision of measurement of paracetamol exposure (eg, reliance on self-reported medication use or prescription databases).[58] In conclusion, the efficacy of paracetamol in hand OA is still uncertain and likely to be small, and this drug is also not free from adverse effects, although for now there is no reason to refrain from prescribing paracetamol, preferably for a limited duration, in selected patients (eg, when oral NSAIDs are contraindicated). Tramadol (with or without paracetamol), was also regarded by the task force as an alternative oral analgesic, although currently no evidence in patients with hand OA is available to support its use.

Chondroitin sulfate may be used in patients with hand OA for pain relief and improvement in functioning

Chondroitin sulfate and glucosamine are among the most widely used over-the-counter nutraceutical products for OA. Chondroitin sulfate was shown to be effective for relief of hand OA symptoms in one well-performed trial, although in patients with knee and hip OA a clinically meaningful effect of glucosamine and chondroitin preparations has not been proven.[59–61] A single report of two (independent) placebo-controlled trials reported structure-modifying effects of chondroitin polysulfate (a preparation that is not commercially available), but not of chondroitin sulfate.[62] However, this evidence was judged unconvincing to promote chondroitin sulfate for structure modification. No placebo-controlled trials of glucosamine have been performed in patients with hand OA. Owing to the limited evidence available to support this recommendation, and even less convincing data from trials in knee and hip OA which led to discouragement of chondroitin sulfate and glucosamine use by NICE, this recommendation was formulated more as a suggestion than a recommendation to use.[63]

In addition to the nutraceuticals discussed here, other so-called Symptomatic Slow Acting Drugs for Osteoarthritis ('SYSADOA') were included in the 2007 recommendation, namely avocado soybean unsaponifiables, diacerhein and intra-articular hyaluronan. Currently, however, there is no evidence for clinical efficacy of these preparations.[16] The task force further agreed that at this moment in OA no drugs are available with disease-modifying properties, and therefore these substances should also not be advocated as such.

Intra-articular injections of glucocorticoids should not generally be used in patients with hand OA, but may be considered in patients with painful interphalangeal joints

This recommendation was completely revised, since the previous recommendation was largely based on expert opinion and new evidence could not confirm a beneficial effect of intra-articular glucocorticoids over placebo in patients with thumb base OA.[64–66] In contrast, in one trial of patients with painful interphalangeal OA, intra-articular glucocorticoid injections were more effective than placebo for pain during joint movement and joint swelling.[67] The formulation 'should not generally be used' was chosen, since the task force recognised that in specific cases where, for example, clear joint inflammation is present, injection with glucocorticoids may still be a therapeutic option. Evidence pertaining specific subgroups that could benefit from intra-articular glucocorticoids, for example, patients with active joint inflammation due to a flare of the disease, is lacking. It is also unknown whether image-guided injections are more beneficial or safer than blind injections, although a Cochrane review of shoulder injections could not establish clinical advantages of guided injection.[68] Injections in small finger joints are preferably performed by a rheumatologist.

Patients with hand OA should not be treated with conventional or biological disease-modifying antirheumatic drugs

This recommendation was newly added, after several studies have emerged demonstrating the lack of efficacy of csDMARD/bDMARD. In clinical practice, severe cases of inflammatory, often erosive, hand OA are occasionally prescribed csDMARDs or even bDMARDs. However, the 2007 recommendations did not include advice on the use of these drugs, and no evidence was available at that time. Trials investigating the efficacy of hydroxychloroquine,[53 69 70] different TNF-inhibitors[71–74] and anti-interleukin-1,[75] could not demonstrate efficacy of these antirheumatic drugs in patients with hand OA. Trials investigating methotrexate, sulfasalazine or colchicine have not been performed. Two trials investigated low-dose oral glucocorticoids (3–5 mg daily), one in combination with dipyridamole, yet reached conflicting conclusions.[76 77] Evidence for short-term use of oral glucocorticoids is therefore still equivocal; at this moment, there is no reason to prescribe glucocorticoids for prolonged periods of time in patients with hand OA.

Surgery should be considered for patients with structural abnormalities when other treatment modalities have not been sufficiently effective in relieving pain. Trapeziectomy should be considered in patients with thumb base OA and arthrodesis or arthroplasty in patients with interphalangeal OA

This recommendation was slightly modified compared with the 2007 recommendation on surgery. Trials with a placebo-controlled or sham-controlled group have not been performed, and so this recommendation remains mostly based on expert opinion.

In the first part of the updated recommendation, treatment failure has now been defined more specifically as 'not sufficiently effective in relieving pain', since surgical interventions are mostly effective to relieve pain, and are less effective in improving function (expert opinion). Surgery should only be considered in persistently symptomatic patients with structural abnormalities despite conventional treatments, including both non-pharmacological and pharmacological therapies. Second, the recommendation does not solely focus on the thumb base joint as before, since surgery can be a viable treatment option in cases with severe painful interphalangeal OA as well.

Surgical interventions vary for the different hand joints. In the CMC-1 joint, trapeziectomy is generally the surgical technique of choice. An updated Cochrane review of the evidence of surgery for thumb base OA found no consistent benefit of one surgical technique over the other, although in general more complicated interventions than simple trapeziectomy led to more adverse effects and were not more effective.[78] Complications reported in the studies included pain, instability, nerve dysfunction, superficial

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wound infections, tendon pulling sensation and chronic regional pain syndrome. Arthroplasty (typically silicone implants) is the preferred surgical technique for the proximal interphalangeal (PIP) joints, with the exception of PIP-2, for which arthrodesis may be considered. Arthrodesis is the recommended approach for the distal interphalangeal joints. No controlled trials of surgery for interphalangeal OA have been published so far.

It is important that patients receive rehabilitation postoperatively. Osteotomy was deleted from the recommendation, as it is an obsolete technique for treating hand OA.

Long-term follow-up of patients with hand OA should be adapted to the patient's individual needs

A recommendation on follow-up was not included in the previous recommendations. Due to the lack of evidence for the cost-effectiveness of long-term follow-up, an evidence-based statement could not be made. Hand OA is a heterogeneous disease, and the spectrum of patients seen with hand OA is diverse, which resulted in a general recommendation. 'Individual needs' that may be taken into consideration when assessing the need for follow-up include severity of symptoms, presence of erosive disease, use of a pharmacological therapy that needs re-evaluation and patient's wishes and expectations.

It was discussed whether long-term follow-up is always indicated for patients with erosive OA. In spite of evidence that these patients have more clinical and structural progression,[79 80] the task force perceived that currently follow-up does not add a benefit. In the absence of a disease-modifying treatment, the goal of follow-up differs from the situation in many other rheumatic diseases. Follow-up will likely increase adherence to non-pharmacological therapies like exercise or orthoses, and provides an opportunity for re-evaluation of treatment (eg, revision of orthoses, or adjustment of pharmacological treatment). For most patients, standard radiographic follow-up is not useful at this moment. Follow-up does not necessarily have to be performed by the rheumatologist. At what moment other health professionals should refer a patient back to the rheumatologist, should be considered at an individual patient level.

Research agenda

A research agenda was developed (table 2).

Table 2 Research agenda for hand OA

Theme	Research questions
Pathophysiology	► Does treatment of inflammation lead to a decrease in structural progression?
Treatment strategy	► Which contextual factors influence treatment effects? ► Assessing efficacy of stratified treatment based on contextual factors.
Trial methodology	► Clear definition of study population to accommodate later subgroup analyses or stratification based on patient characteristics.
Outcomes	► Evaluation of outcome measures in hand OA, and use of existing outcome core sets for future hand OA trials. ► Cost-effectiveness studies. ► Defining treatment targets for disease-modifying drugs.
Education	► Evaluation of efficacy of education without concomitant exercise. ► Definition of the desired content of education.
Exercise	► Assessment of most effective type of hand exercises, most optimal method of delivery and most optimal frequency. ► Assessment of methods to increase adherence to exercise.
Orthoses	► Assessment of orthosis design (material, which joints are supported), and instructions or frequency for use of orthoses. ► Evaluation of daytime orthoses, night-time orthoses and a combination of daytime and night-time orthoses. ► Placebo-controlled trial of orthoses for thumb base OA. ► Evaluation of effect of use of orthoses on CMC-1 subluxation.
Topical treatments	► Another placebo-controlled trial of topical NSAID.
Oral analgesics	► Placebo-controlled trial of paracetamol. ► Placebo-controlled trial of tramadol.
Nutraceuticals	► Placebo-controlled trial of glucosamine. ► Another placebo-controlled trial of chondroitin sulfate, also to assess possible effect on structural damage.
Intra-articular therapies	► Placebo-controlled trial of intra-articular glucocorticoids specifically in CMC-1 joints with OA inflammation. ► Image-guided injection vs blind injection.
DMARDs	► Placebo-controlled trial of methotrexate. ► Placebo-controlled trial of low dose oral glucocorticoids.
Surgery	► Randomised controlled trial of most commonly used surgical interventions. ► Assessment of best timing of referral to surgery. ► Evaluation of whether early non-pharmacological interventions may prevent or delay surgery.
Follow-up	► Investigation of trajectories in hand OA to define subgroups.
Implementation	► Determination of optimal implementation of the guidelines in people with hand OA.

CMC-1, first carpometacarpal; DMARDs, disease-modifying antirheumatic drugs; OA, osteoarthritis.

DISCUSSION

This is the first update of the EULAR recommendations for the management of hand OA, containing five overarching principles and 10 recommendations. After a decade, it was timely to update the recommendations, as many new studies had emerged during this period. In light of this new evidence, many of the 2007 recommendations were modified and new recommendations were added. Furthermore, recommendations were formulated as recommendations rather than 'statements' reflecting the state of the evidence and/or expert opinion.

In this update, two patient research partners with hand OA were included as active members of the task force, while the 2007 task force did not include patient research partners. This is an important improvement, since patients are one of the important target-users of these recommendations, and in evidence-based clinical decision making, the patient perspective is valued as equally important to research evidence and clinical expertise.[81]

New in the 2018 update is also the use of overarching principles. This is in line with other EULAR sets of management recommendations. Some of the 2007 recommendations were in retrospect already more an overarching principle, and were (modified and) included in the 2018 update as such, for example, statements regarding individualised treatment, and combination of non-pharmacological and pharmacological treatment modalities.

Moreover, the 2018 update of the SLR summarising the evidence for the recommendations, is published as a separate manuscript.[16] As pointed out in their discussion, Zhang *et al* did perform a systematic search of the literature to underpin the recommendations, but rather than reviewing all possible treatments, a limited number of key propositions were highlighted. The publication of the complete SLR, including a detailed description of its methodology and results, provides the interested reader with a full update of the currently available evidence concerning the management of hand OA and provides

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more insight in the size of the effects of different interventions compared with placebo or control treatment. It is important to note that the recommendations as presented in table 1 cannot be read and interpreted without the accompanying text, and this manuscript and the separately published SLR form an integral part, and should be considered together.

Guidelines for the management of OA from other large (international) societies, including the 2012 ACR recommendations and the NICE guidelines, mainly focus on large joint OA (ie, knee and hip).[10 63] However, these recommendations cannot readily be extrapolated to the situation of OA in the hand because of the unique functionality of the hands compared with large joints, and emerging evidence for different risk factors and possibly even pathophysiological mechanisms of OA at different joint sites.

These recommendations are targeted at all health professionals who care for patients with hand OA. Since hand OA is a prevalent disease encountered by a variety of healthcare providers in primary and secondary care, this not only includes rheumatologists, but also for example general practitioners, orthopaedic and plastic surgeons, occupational and physical therapists and rehabilitation physicians. Furthermore, these recommendations aim to inform patients about their disease to support shared decision-making, as well as students. Other targeted stakeholders include pharmaceutical industry, policy makers and health insurance companies.

Efforts to implement these recommendations will be made by dissemination across national societies, online and by presentations in (inter)national congresses and educational sessions for healthcare providers. A slide deck to facilitate dissemination will be provided on the EULAR website. Evidence of optimal systematic implementation is lacking and this was highlighted in the research agenda.

Although a relatively long period passed between the first set of recommendations and the current update, it is expected that the next update of the recommendations may be needed sooner, as the field of hand OA is growing. Advances in research of OA pathophysiology as well as outcome measurement, increase the likelihood of finding new therapeutic options. The next update should be undertaken when sufficient new data are available, either on the current treatment options, or on new therapies.

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2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

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ABSTRACT

To update the European League Against Rheumatism (EULAR) recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD) published in 2011. Four systematic literature reviews were performed regarding the incidence/prevalence of vaccine-preventable infections among patients with AIIRD; efficacy, immunogenicity and safety of vaccines; effect of anti-rheumatic drugs on the response to vaccines; effect of vaccination of household of AIIRDs patients. Subsequently, recommendations were formulated based on the evidence and expert opinion. The updated recommendations comprise six overarching principles and nine recommendations. The former address the need for an annual vaccination status assessment, shared decision-making and timing of vaccination, favouring vaccination during quiescent disease, preferably prior to the initiation of immunosuppression. Non-live vaccines can be safely provided to AIIRD patients regardless of underlying therapy, whereas live-attenuated vaccines may be considered with caution. Influenza and pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD. Tetanus toxoid and human papilloma virus vaccination should be provided to AIIRD patients as recommended for the general population. Hepatitis A, hepatitis B and herpes zoster vaccination should be administered to AIIRD patients at risk. Immunocompetent household members of patients with AIIRD should receive vaccines according to national guidelines, except for the oral poliomyelitis vaccine. Live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers treated with biologics during the second half of pregnancy. These 2019 EULAR recommendations provide an up-to-date guidance on the management of vaccinations in patients with AIIRD.

INTRODUCTION

Patients with autoimmune inflammatory rheumatic diseases (AIIRD) have an increased burden of infections, attributed to the underlying autoimmune disease,[1–4] comorbidities[3 5] and immunosuppressive therapy, including glucocorticoids (GCs), disease-modifying antirheumatic drugs (DMARDs): conventional synthetic (csDMARDs), biological (bDMARDs) and targeted synthetic DMARDs (tsDMARDs).[3 6 7] As the 'treat to target' principle currently guides an intensive immunosuppressive therapy aimed at remission in most rheumatic diseases,[8–10] these therapies are commonly applied, in particular at early disease stages. Thus, prevention of infections is crucial in the management of patients with AIIRD.

Vaccination prevents infections by inducing and/or enhancing protective immunity. Vaccination is particularly important in AIIRD patients, potentially translating into a lower rate of hospital admissions due to infections, emergency room visits and the rate of invasive infectious diseases.[11] Yet, the AIIRD population universally suffers from a suboptimal uptake of vaccinations,[12–19] in part due to a low rate of referral for vaccination by rheumatologists[20] and other treating physicians,[21] indicating that further interventions are needed to raise the awareness for vaccination among the rheumatology community and involved healthcare professionals. Another important factor for a low vaccination rate relates to concerns about efficacy, immunogenicity and safety of vaccinations,[15] an important issue to be addressed by upcoming evidence.

Our aim was to update the present European League Against Rheumatism (EULAR) recommendations for vaccination in patients with AIIRD published in 2011 and to incorporate the new evidence on the incidence/prevalence of vaccine preventable infections (European League) among AIIRD patients, along with efficacy, immunogenicity and safety of vaccines provided to AIIRD patients under a wide range of immunosuppressive therapies. The update was conducted in line with the standard operating procedures (SOP) of the EULAR,[22] combining evidence from clinical studies and expert opinion. Our recommendations target all healthcare professionals involved in the care for patients with AIIRD.

METHODS

Development of recommendations

The present update of the EULAR recommendations for vaccination in patients with AIIRD was a combined project for the adult and paediatric AIIRD populations. Following the 2014 updated EULAR SOP,[22] the convenor (OE) first formed the

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Box 1. Research questions.

- What is the incidence or prevalence of vaccine-preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD)?
- What is the efficacy, immunogenicity and safety of available vaccines in adult AIIRD patients?
- Are vaccines efficacious and immunogenic in adult AIIRD patients, treated with immunosuppressive agents and disease-modifying antirheumatic drugs?
- What is the effect of vaccination of household of AIIRD patients, including newborns, on the prevention of vaccine preventable diseases and safety of the patients?

task force with a steering committee. The steering committee included the convenor (OE), co-convenor (ULM), methodologists (JvL and RL), three fellows who performed the systematic literature reviews (SLRs) (VF, CR, MH), one expert rheumatologist (MB) and one specialist in infectious diseases (SvA). The steering committee defined the research questions for the SLRs (Box 1) and organised a one-and-a-half-day meeting of the task force. Participants of the adult task force meeting represented seven European countries and Israel, included 10 adult rheumatologists, four clinical immunologists, one infectious disease specialist, one paediatrician/rheumatologist, two delegates of the EULAR young rheumatologists' network Emerging EULAR NETwork, one health professional in rheumatology (HPR) and two patients. Three fellows (VF, CR, MH) performed four SLRs covering the incidence of VPI, the efficacy, immunogenicity, safety of vaccination in patients with AIIRD, the effect of DMARDs on vaccination response and the effect of vaccination of household of AIIRDs patients, including newborns, on the prevention of VPI and safety of the patients. These SLRs focused on the studies published after the locking date of the SLRs for the previous update, that is, October 2009. MEDLINE (via PubMed), EMBASE and Cochrane were searched from 1 October 2009 to 1 August 2018. As search terms, the medical subject headings (MESH) terms for the defined AIIRD, immunosuppressive medications and vaccines were combined (Box 2). Only articles in English were included. Other papers that were considered relevant in the opinion of the experts could be added.

The first part of the meeting was shared by both adults and paediatric members of the task force, during which the preliminary results of the four SLRs were presented. Following the presentation, the group split in two in order to formulate the separate updated recommendations for vaccination in adults and children with AIIRD. In the adult group, the convenor (OE) proposed the wording of each recommendation. Each recommendation was discussed within the group and formulation was modified until agreement was reached among the members. In the second part of the meeting, the two groups rejoined and reviewed the two sets of recommendations, mainly in order to verify that there was no major discrepancy between them. Minor changes were made following this presentation and approved by all the members of the task force. The second meeting of the task force was then organised and included the presentation of the updated SLRs concerning the adult population with AIIRD. The results of the SLRs are reported in two articles, submitted for publication to RMD Open. Each recommendation was discussed and modified when necessary, followed by the second round of voting by all the members of the task force.

Six overarching principles and nine recommendations were formulated (tables 1 and 2). For each statement, the available evidence was critically appraised and the strength of the recommendations (SoR) was determined following the standards of the

Box 2. Definition of autoimmune inflammatory rheumatic diseases (AIIRD), immunosuppressive agents and vaccines included in the literature search and recommendations

Autoimmune inflammatory rheumatic diseases

- Rheumatoid arthritis, juvenile idiopathic arthritis
- Adult Still's disease
- Systemic lupus erythematosus, Sjogren's syndrome, antiphospholipid syndrome
- Systemic sclerosis, mixed connective tissue disease
- Polymyositis, dermatomyositis, antisynthetase syndrome, clinically amyopathic dermatomyositis, inclusion body myositis, eosinophilic myositis, eosinophilic fasciitis
- Psoriatic arthritis, spondyloarthropathy
- Polymyalgia rheumatica
- Giant cell arteritis, Takayasu arteritis
- Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis: granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- Polyarteritis nodosa
- Cryoglobulinemic syndrome
- Anti-glomerular basement membrane (GBM) antibody disease (Goodpasture disease)
- Behcet disease
- Relapsing polychondritis
- Periodic fever syndromes
- Familial Mediterranean fever

Immunosuppressive agents

- Glucocorticoids
- Synthetic disease-modifyingantirheumatic drugs (DMARDs): methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine
- Mycophenolic acid preparations
- Calcineurin inhibitors: cyclosporine, tacrolimus
- Alkylating agent: cyclophosphamide
- Biologic DMARDs: infliximab, etanercept, adalimumab, certolizumab, golimumab abatacept, tocilizumab, rituximab secukinumab, ixekizumab belimumab anakinra, canakinumab
- Targeted synthetic DMARDs: tofacitinib, baricitinib

Vaccines

Inactivated

- Diphtheria, hepatitis A, hepatitis B, Haemophilus influenzae b, human papillomavirus, influenza, Neisseria meningitides, pertussis, parenteral poliomyelitis, *streptococcus pneumoniae* (polysaccharide and conjugated), tetanus toxoid, tick-borne encephalitis, parenteral typhoid fever

Live-attenuated

- Measles, mumps, oral poliomyelitis, oral typhoid fever, varicella zoster, yellow fever

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Table 1 Overarching principles for vaccination in adult patients with AIIRD

	Overarching principles	Level of Agreement (%)
1.	The vaccination status and indications for further vaccination in patients with AIIRD should be assessed yearly by the rheumatology team.	100%
2.	The individualised vaccination programme should be explained to the patient by the rheumatology team, providing a basis for shared decision-making, and be jointly implemented by the primary care physician, the rheumatology team and the patient.	94%
3.	Vaccination in patients with AIIRD should preferably be administered during quiescent disease.	94%
4.	Vaccines should preferably be administered prior to planned immunosuppression, in particular B cell depleting therapy.	100%
5.	Non-live vaccines can be administered to patients with AIIRD also while treated with systemic glucocorticoids and DMARDs.	100%
6.	Live-attenuated vaccines may be considered with caution in patients with AIIRD.	53%

AIIRD, autoimmune inflammatory rheumatic diseases; DMARDs, disease-modifying antirheumatic drugs.

Table 2 Recommendations for vaccination in adult patients with AIIRD with level of evidence for the incidence/prevalence of VPI, efficacy, immunogenicity and safety of vaccines, strength of recommendations (SoR) and level of agreement for each recommendation

Recommendation	Infection rate	Efficacy	Immuno-genicity	Safety	SoR*	Level of agreement: average/ range (0–10), %≥8
1. Influenza vaccination should be strongly considered for the majority of patients with AIIRD.	2b	2b	2a	2b	B	9.4 7–10 93%
2. Pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD.	2b	4	2a	4	C	8.7 6–10 93%
3. Patients with AIIRD should receive toxoid tetanus vaccination in accordance with recommendations for the general population. Passive immunisation should be considered for patients treated with B cell depleting therapy.	NA	NA	2b	4	B D	9.5 8–10 100%
4. Hepatitis A and hepatitis B vaccination should be administrated to patients with AIIRD at risk. In specific situations booster or passive immunisation is indicated.	HAV – NA HBV 2b	NA	2b	4	B C	9.6 8–10 100%
5. Herpes zoster vaccination may be considered in high-risk patients with AIIRD.	2b	2b	2b	4	B	9.1 7–10 93%
6. Vaccination against yellow fever should be generally avoided in patients with AIIRD.	NA	NA	2b	4	D	9.2 6–10 85.7%
7. Patients with AIIRD, in particular patients with SLE, should receive vaccinations against HPV in accordance with recommendations for the general population.	2b	NA	2b	4	C	9.5 8–10 100%
8. Immunocompetent household members of patients with AIIRD should be encouraged to receive vaccines according to national guidelines with the exception of the oral polio vaccines.	NA	NA	NA	NA	D	9.1 7–10 93%
9. Live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers treated with biologics during the second half of pregnancy.	NA	NA	NA	NA	D	9.5 8–10 100%

*The strength of recommendation was primarily based on the efficacy data. If no efficacy data were available, immunogenicity was used as a major outcome. When immunogenicity outcomes did not directly correlate with protection, the strength of recommendation was downgraded. Few recommendations were primarily based on safety (especially live-attenuated vaccines) and here, the safety outcomes determined the strength of the recommendation.
AIIRD, autoimmune inflammatory rheumatic diseases; HAV, hepatitis A virus; HBV, hepatitis B virus; HPV, human papilloma virus; NA, non-available; SLE, systemic lupus erythematosus.

Oxford Centre for Evidence Based Medicine.[23] (online supplementary file 1)

After the second meeting, the final version of recommendations was disseminated among the members of the task force who electronically voted for agreement for each of the principles and recommendations. Each statement was separately voted on and given a score from 0 (absolutely no agreement with the proposed recommendation) to 10 (maximal possible support for the recommendation). The level of agreement for each recommendation was based on the mean vote score.

The final manuscript was drafted after the second meeting of the task force. The manuscript was structured according to the Appraisal of Guidelines for Research & Evaluation II principles,[22 24] reviewed, revised and approved by all the task force members, followed by final review and approval by the EULAR Executive Committee before submission to the journal.

Definitions

In the field of vaccination, several outcome measures are important. First, the capacity of vaccinations to prevent infections, referred to as 'efficacy'. Often, humoral responses to vaccines are considered as surrogate endpoints for efficacy, in particular for rare infections, that otherwise would require infeasible trials needing a very large number of patients to prove the vaccine's efficacy. The capacity of vaccines to induce humoral and/or cellular immune responses is referred to as 'immunogenicity'. These immune responses may correlate with clinical

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efficacy for some vaccines, but not necessarily. This should be taken into account when interpreting the available evidence (primarily on immunogenicity) for these recommendations.

The SoR was primarily based on the level of evidence for efficacy of vaccination. In vaccine studies with only immunogenicity outcomes, the SoR was established based on the surrogate outcome (immunogenicity). In case there was no direct correlation between the immunogenicity outcomes and the level of protection, the SoR was downgraded.

Finally, the safety of vaccines is of great importance. Safe vaccination implies that vaccination has no severe adverse effects and does not aggravate the underlying disease. Especially for live-attenuated vaccines, safety is a major concern. For these vaccines, the safety outcomes primarily determined the SoR. The level of available evidence concerning efficacy, immunogenicity and safety provided the data was available, is presented for each recommendation.

RESULTS

Overarching principles

The task force endorsed the presentation of six general principles for vaccination of patients with AIIRD as overarching (table 1). Three new overarching principles were formulated. The other three principles originated from the recommendations #2 to #4 published in the 2011 version and were incorporated in the overarching principles due to their importance and generic nature.[25] The level of agreement of each overarching principle is presented in table 1.

The vaccination status and indications for further vaccination in patients with AIIRD should be assessed yearly by the rheumatology team

The force task endorsed an annual assessment of the vaccination status by the treating rheumatology team as a central principle guiding vaccinations in patients with AIIRD, constituting an overarching principle rather than a recommendation. In the 2011 version, the first recommendation referred to the assessment of the vaccination status of patients with AIIRD in the initial workup, without defining the responsible healthcare provider. The current version emphasises the need for an *annual assessment*, delegating the responsibility to the treating rheumatologist or rheumatology team. The rheumatology team has an extended knowledge and expertise encompassing all aspects of AIIRD, including related treatment modalities applied to an individual patient. For patients with AIIRD, the treating rheumatology team commonly manages their medical care, communicates with a primary care physician and coordinates a multidisciplinary network when required. As stated in the 2011 version, an inventory of a vaccination history, adverse events and flares of the underlying AIIRD following earlier vaccinations should be included in the assessment and turned into the standard of care of patients with AIIRD.

The individualised vaccination programme should be explained to the patient by the rheumatology team, providing a basis for shared decision-making, and be jointly implemented by the primary care physician, the rheumatology team and the patient

This is a newly formulated principle, strongly endorsed by the patient representatives of the task force and supported by the other members. Shared decision-making and consideration of patient's needs, concerns and preferences have received the most prominent recognition in treatment of chronic diseases, as reflected in the updated EULAR recommendations.[8–10] Identifying barriers to immunisation and addressing patients' fears and concerns regarding adverse effects is a crucial step toward adherence with any immunisation programme. Having access to evidence-based information about vaccines and comprehension of risks and benefits of vaccination, enables patients to make a deliberate decision regarding the offered vaccination programme. The rheumatology team should inform patients about the risk of infections and the indications for vaccinations, educate patients about the risk/benefit ratio of vaccines and encourage patients to adhere to the appropriate vaccination schedule. Indeed, surveys among patients with AIIRD demonstrated that better knowledge about vaccination and recommendation for vaccination by a treating specialist were positively associated with improved vaccine uptake.[15 26] Communication between the rheumatology and primary care teams further supports the implementation of the vaccination programme. A large survey of rheumatoid arthritis (RA) patients in the UK revealed that the majority of vaccination was undertaken in primary care,[27] supporting collaboration between primary and secondary care to maximise vaccine uptake.

Vaccination in patients with AIIRD should preferably be administered during quiescent disease

This statement, listed as the second recommendation in the 2011 version, was shifted into the third overarching principle. The rationale for this decision was the shared opinion by the majority of the members that this important message would benefit from being a fundamental general principle. Indeed, most vaccination studies conducted in the AIIRD population included patients with quiescent disease.[28–33] The number of studies with AIIRD patients immunised at the active disease stage is too low to draw the conclusion that vaccinations during active phases of disease are effective or safe. One study has directly addressed the impact of underlying disease activity on the immunogenicity of vaccination.[34] In this study, patients with juvenile systemic lupus erythematosus (SLE) with high SLE activity had reduced seroconversion rates to influenza A H1N1 vaccination. Notably, in a study of 340 RA patients, high disease activity levels did not preclude immune response to influenza A H1N1 vaccination.[35] Yet, based on the limited knowledge on safety and immunogenicity of vaccinations in patients with active disease, vaccinations are preferentially administered during quiescent disease, according to expert opinion. In patients with active disease, immunisation should not be precluded and considered on the individual basis.

Vaccines should be preferably administered prior to planned immunosuppression, in particular B cell depleting therapy

This important concept, based on the fourth recommendation in the 2011 version, was further expanded to the initiation of csDMARDs, bDMARDs and tsDMARDs, prompting an early vaccination policy to ensure the optimal response to vaccines. Yet, it is important to emphasise that the intention of this principle is *not* to delay a necessary immunosuppressive treatment in severe cases. In such cases, initiation of the indicated immunosuppressive treatment is the main priority rather than early administration of vaccines.

A clear consensus was reached on the suppressive effect of rituximab (RTX) on humoral response to influenza and pneumococcal vaccination in patients with RA,[36–47] spondyloarthropathies (SpA)[42] and SLE,[48] explaining the rationale to provide vaccination *prior to the administration of rituximab*. Other bDMARD therapies have a variable impact on the response to

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immunisation in the AIIRD population, with the majority of patients reaching a satisfactory serological response. The effect of specific DMARDs is broadly discussed in the extended SLR (submitted for publication in RMD Open).

In summary, vaccines should be ideally administered *before* the planned immunosuppression, with the emphasis on B cell-depleting biological therapy. In case of non-immunised patients on B cell-depleting therapy, vaccination should be provided at the following time window: at least *6 months after* the administration and *4 weeks before the next course* of B cell-depleting therapy, based on the state of clinical practice. In cases when this time window for immunisation is not possible, vaccination may be considered under B-cell depleting therapy, taking into consideration a potential suboptimal response to vaccine.

Non-live vaccines can be administered to patients with AIIRD during the use of glucocorticoids and DMARDs

Originally presented as the fourth recommendation in the 2011 version, this statement has been modified and upgraded to an overarching principle, in light of compelling evidence of the overall adequate efficacy and safety of vaccination during the use of GC and/or both csDMARDs, bDMARDs and tsDMARDs in a variety of rheumatic diseases. Accumulating data over the recent years have supported the administration of influenza, pneumococcal, tetanus toxoid, hepatitis B virus (HBV), hepatitis A virus (HAV), and human papilloma virus (HPV) vaccines to patients with AIIRD under immunosuppressive therapy. In the majority of studies adequate immunoprotection was achieved, with no major safety signals, though the follow-up period was short in most studies. The details of the relevant studies are provided in the SLR by Rondaan *submitted for publication in Open RMD*.

Live-attenuated vaccines may be considered with caution in patients with AIIRD

Administration of live-attenuated vaccines in patients with AIIRD warrants special attention. In the 2011 version, the third recommendation stated that live-attenuated vaccines should be *avoided* whenever possible in immunosuppressed patients with AIIRD. In light of the new evidence and experience on administrating certain live-attenuated vaccines in patients with AIIRD, the task force has extensively discussed the modification of the original statement to formulate it in a more permissive mode. Agreement was reached to incorporate the new evidence in the updated recommendations with a detailed explanation of the rationale and the new evidence. In general, live-attenuated vaccines should be avoided in patients under immunosuppressive therapy, as these vaccines contain live-attenuated micro-organisms that theoretically might cause infections in the susceptible AIIRD population. Based on expert opinion, the preferable time window for vaccination with live vaccines is *4 weeks prior to treatment initiation*, based on the state of clinical practice. However, vaccinations such as measles, mumps, rubella (MMR) and live-attenuated herpes zoster vaccines may be an exception.

Following the Centers for Disease Control and Prevention (CDC) recommendations, the definition of the 'immunosuppressive therapy' includes GC usage for ≥2 weeks in dosages equivalent to prednisone of 20 mg/d or 2 mg/kg body weight are considered immunosuppressive, as is methotrexate (MTX) ≥0.4 mg/kg/week, azathioprine ≥3.0 mg/kg/day or 6-mercaptopurine ≥1.5 mg/kg/day, whereas dosages below these levels may be considered as a 'low grade' immunosuppression. The level of immunosuppression in case of a long-term treatment with low dose GC requires further investigation. In the field of rheumatology, bDMARDs and tsDMARDs are likewise defined as immunosuppressive therapy.

The evidence on MMR is mainly derived from the observational data in the paediatric population of patients with AIIRD. With regard to immunogenicity, a retrospective study from the Netherlands reported a long-term persistent seroprotection for measles in a large group of patients with juvenile idiopathic arthritis (JIA).[49] The use of GCs or MTX did not influence the antigen-specific antibody concentration or seroprotection rates. Consistently, a similar outcome was reported in a small retrospective study performed in paediatric SLE patients in Brazil.[50] A prospective nested case-control study from Germany also reported a protective humoral response following 6 months after measles revaccination in 15 patients with JIA, treated with either low-dose MTX therapy alone or in combination with etanercept.[51] Regarding safety, no increase in disease activity, measles flare or severe serious infections were seen, including JIA patients using etanercept.[51] A randomised, open-label study from the Netherlands confirmed an appropriate immunogenicity and safety of the MMR booster provided to JIA patients, including 60 patients using MTX and a small number of patients using bDMARDs.[52] Based on these safety data of the MMR booster vaccination, the measles virus booster vaccine (as opposed to neo-immunisation) can be considered in AIIRD patients on low grade of immunosuppression at risk of contracting measles infection (for example, travellers).

Concerning vaccination against herpes zoster (HZ), two studies evaluated the safety of the live-attenuated zoster vaccine in AIIRD patients using immunosuppressive drugs. A large cohort study of Medicare beneficiaries 60 years and older with AIIRD, treated with immunosuppressive therapies, including bDMARDs, did not show any increase in the incidence of herpes zoster during the first 42 days after vaccination.[53] Live-attenuated HZ vaccine was safely provided to a small cohort of SLE patients (n=10), followed for 12 weeks.[54] Based on these studies, the live-attenuated HZ vaccine may be considered in patients at risk. A non-live virus vaccine is now available in some countries. Both vaccines are discussed in the recommendation #5 below.

In summary, live-attenuated vaccines should be avoided during immunosuppression, with a possible exception of a cautious use of MMR booster and HZ vaccine under special circumstances, as discussed above.

Recommendations

A total of nine recommendations have been formulated. For each recommendation, the level of evidence for the incidence/prevalence of VPI in AIIRD, and efficacy/immunogenicity/safety of vaccination were stated, when available, followed by the strength of recommendation and the level of agreement (table 2). Six of these recommendations concerning influenza, pneumococcal, tetanus toxoid, HAV, HBV as well as HPV vaccinations originated from the 2011 recommendations with some modifications. Three recommendations (former #10, #12 in the 2011 version) concerning vaccination in hyposplenic/asplenic patients with AIIRD, BCG vaccination and travelling patients with AIIRD were deleted. The task force decided that the first two topics became irrelevant in a daily rheumatology practice. The recommendation for the travelling patients with AIIRD (former #13) to follow the national guidelines was omitted due to being non-specific. Two new recommendations (#8, #9) were formulated encompassing the vaccination in household members of patients with AIIRD and newborns treated with biologics during pregnancy. An SLR was performed on these topics which

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disclosed no relevant papers. Thus, these recommendations were based on expert opinion.

Influenza vaccination should be strongly considered for the majority of patients with AIIRD

This recommendation, listed #5 in the 2011 version, remained essentially unchanged, except for the remark that the vaccine should be considered for the *majority* of patients and not *all* patients. Patients with AIIRD have a higher risk of contracting influenza compared with the general population.[55–57] The task force panel has extensively discussed the scope of patients for whom the vaccine should be recommended. As there is a substantial variability in national guidelines for influenza vaccination, ranging from the whole population vaccination in the USA to age-based and risk-based vaccination in other countries, the panel has taken into consideration different epidemiological and clinical aspects of influenza vaccination in patients with AIIRD. To date, there is no compelling epidemiological evidence to justify a universal influenza vaccination for the whole population of patients with AIIRD. For example, young patients with ankylosing spondylitis, treated with non-steroidal anti-inflammatory drugs only, are not considered immunosuppressed and thus are not at increased risk of influenza-related morbidity. Yet, the majority of the AIIRD population, in particular patients treated with immunosuppressive therapy, seems to benefit from the vaccine.[33 58 59]

Regarding efficacy, seasonal trivalent subunit influenza vaccination has been shown to reduce the incidence and bacterial complications of influenza, admissions for and mortality from influenza/pneumonia in AIIRD.[60–63] Most studies have focused on immunogenicity as surrogate outcome for efficacy. Influenza vaccination has been shown to be immunogenic in patients with RA, SLE, ANCA-associated vasculitis (AAV), SSc, and PsA, treated with all classes of DMARDs,[33 59 64–98] except for rituximab.[37 41 43 99 100] Temporary discontinuation of MTX was shown to improve immunogenicity of seasonal influenza vaccination in patients with RA, with the best results when MTX was suspended for 2 weeks before and 2 weeks after vaccination.[101 102] However, it is currently not recommended to stop MTX before or after vaccinating for influenza. Adverse events of influenza vaccination in patients with AIIRD seem comparable to those in healthy controls, although there are no studies that are sufficiently powered with regard to safety.[28 33 41 43 64 65 69 73–78 81 83–86 88–90 92 94–96 99 103 104]

Most studies investigating immunogenicity and safety of the pandemic monovalent influenza vaccine found reduced immunogenicity in AIIRD patients (mostly RA and SLE) and on most immunosuppressive medications, although protective antibody levels were reached in the majority of patients,[34 35 38 40 59 89 105–116] except for those treated with rituximab and abatacept.[38 42 117] A second booster dose of vaccine was shown to improve immunogenicity, leading to levels of seroprotection comparable to healthy controls.[40 42 118] This has also been shown in SLE patients who received seasonal influenza vaccine for the first time.[29]

Following vaccination with both seasonal and pandemic influenza vaccines, the disease activity was stable in the majority of studies and only mild adverse events, comparable with healthy controls, were reported.[34 35 38 40 59 89 105–109 113–116 119] Based on the data of increased risk and morbidity of influenza infection in AIIRD patients, in combination with studies showing a decrease in influenza infections following vaccination, and a large body of evidence proving good influenza vaccine immunogenicity and safety in AIIRD patients, influenza vaccination should be strongly considered for the majority of patients.

Pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD

This recommendation, listed #6 in the 2011 version, has been modified defining the scope of candidates to pneumococcal vaccine as the 'majority' of patients with AIIRD, in order to target patients at risk of pneumococcal disease. The task force panel has extensively discussed the types of pneumococcal vaccine, timing of vaccine administration, the scope of patients who will mostly benefit from vaccination and cost-effectiveness of the vaccine in order to target AIIRD patients at risk of pneumococcal disease.

The risk of pulmonary infection is particularly high for patients with AIIRD. In a study of US veterans with RA, the highest rate of hospitalisation for infection was due to pneumonia (37%).[120] RA and SLE were identified as additional at-risk conditions for pneumococcal disease.[121] The incidence of invasive pneumococcal infection in SLE patients was 13 times higher compared with the Dutch general population.[122]

Two pneumococcal vaccines are now available: the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13). Regarding efficacy, a randomised double-blind trial on the clinical efficacy of PPSV23 in preventing pneumonia in RA patients did not demonstrate an increased efficacy of the vaccine over placebo.[123] On the other hand, a retrospective study on the long-term effect of PPSV23 in RA patients treated with MTX showed a relative risk of 9.7 to develop pneumonia in non-vaccinated patients.[124] The humoral immunogenicity and safety of the PPSV23 has been demonstrated in RA,[64 87 125–129] SLE,[130–132] and to a limited extent in SpA and others.[133] The long-term immunogenicity of PPSV23 has been evaluated in two studies, in RA patients treated with MTX[124] and biologics, respectively.[134] Both have shown a long-term duration of protective antibodies, up to 7 years. The immunogenicity and safety of PCV13 has been evaluated in small groups of patients with RA and found to induce an appropriate humoral response,[135] although reduced under MTX,[136] in SLE[137] and systemic vasculitis patients.[138] None of the above-mentioned studies raised any safety concerns except for patients with cryopyrin associated periodic syndromes (CAPS), who may develop severe local reactions and systemic reactions to PPSV23.[139]

Stepwise pneumococcal vaccination, a PCV13 prime-PPSV23 boost strategy, with an interval of at least 8 weeks between the two vaccinations, is now recommended based on the CDC and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommendations for young children, adults above 65 years old and patients at risk for pneumococcal disease (table 3). This is mainly based on expert opinion. Evidence from studies conducted in the general population[140 141] and patients with HIV[142] showed an augmented immunogenic response following the combined vaccination. On the other hand, the evidence for the efficacy of the combination of PCV13 and PPSV23 in patients with AIIRD is insufficient. A randomised controlled study in RA patients evaluated the serological response to PCV13 followed by PPSV23 after 16 to 24 weeks. The study demonstrated an adequate response (87% and 94% in RA patients on bDMARDS and csDMARDS, respectively), with a significantly decreased response in patients treated with RTX. A prime boosting strategy with PCV13 did not improve the response.[45] However, long-term follow-up studies addressing persistence of the humoral response and immunological memory are not available yet.

In view of the increased risk of non-invasive and invasive pneumococcal disease in patients with AIIRD, along with good

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Table 3 Schedule of administration of pneumococcal vaccine in AIIRD patients under immunosuppressive therapy based on the CDC recommendations

History of prior vaccination	Schedule for administration of PCV13 and PPSV23
None or unknown	Administer PCV13 followed in 8 weeks by PPSV23 #1. Administer PPSV23 #2 at least 5 years after PPSV23 #1.
One dose PPSV23; zero or unknown PCV13	Administer PCV13 at least 1 year after PPSV23 #1. Administer PPSV23 #2 at least 5 years after PPSV23 #1 and at least 8 weeks after PCV13.
Zero or unknown PPSV23; one dose PCV13	Administer PPSV23 #1 at least 8 weeks after PCV13. Administer PPSV23 #2 at least 5 years after PPSV23 #1.
One dose PPSV23; one dose PCV13	Administer PPSV23 #2 at least 5 years after PPSV23 #1 and at least 8 weeks after PCV13.
Two doses PPSV23; 0 or unknown PCV13	Administer PCV13 at least 1 year after PPSV23 #2.

Reference:http://www.immunize.org/catg.d/p3075.pdf

AIIRD, autoimmune inflammatory rheumatic diseases; CDC, Centers for Disease Control and Prevention; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

efficacy, immunogenicity and favourable safety profile of pneumococcal vaccines in the healthy population, and in line with the present recommendations of the CDC[143 144] and the ESCMID,[145] pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD. Pneumococcal vaccination should be considered carefully in patients with CAPS given the potential risks of adverse events. The task force does not have a reason to recommend a specific pneumococcal vaccine based policy based on the present data on efficacy, immunogenicity and safety of available pneumococcal vaccines. Costs of vaccines may play a role in the decision of the vaccine choice.

Patients with AIIRD should receive tetanus toxoid vaccination in accordance to recommendations for the general population. Passive immunisation should be considered for patients treated with B cell depleting therapy.

The content of this recommendation remained essentially unchanged (*reference recommendation #7 in the 2011 version*), except of rephrasing of the second statement.

No studies evaluated infection rates of tetanus after vaccination. Humoral response to tetanus vaccination strongly correlates with disease prevention and therefore can be used as a clinical outcome measure. In general, patients with AIIRD are recommended to receive tetanus toxoid vaccination in accordance to recommendations for the general population.

Patients with RA and SLE show a satisfactory immunogenicity for tetanus toxoid vaccination comparable with healthy controls.[146–148] This also holds true for patients with RA on immunosuppressive drugs,[128 149] including those treated with rituximab 24 weeks earlier.[36] Treatment with belimumab did not affect the ability of patients with SLE to maintain antibody titers to previous tetanus immunisation.[150] Although no data are available regarding the efficacy of tetanus toxoid vaccine under the influence of B cell depleting therapy, the efficacy is assumed to be decreased in this situation, based on the data extrapolation from other vaccines. Therefore, passive immunisation with tetanus immunoglobulins should be considered in case of a high-risk exposure to tetanus in patients treated with B cell therapy, according to the expert opinion.

Hepatitis A and hepatitis B vaccines should be administered to AIIRD patients at risk — in specific situations, booster or passive immunisation is indicated

The original recommendation on HAV and HBV vaccination (#11 in the 2011 version) has been expanded regarding the indication for a booster or passive immunisation in specific cases. No data on the incidence/prevalence of HAV in AIIRD is available. Patients with AIIRD at risk of contracting hepatitis A are recommended to receive vaccination against hepatitis A. Patients at risk include HAV-seronegative patients travelling to or resident in endemic countries. Data on the vaccine efficacy are lacking, but there is a strong correlation between antibody concentrations and seroprotection against infection. It should be emphasised that, as opposed to strong immunogenicity in healthy individuals, a single dose of HAV vaccine does not seem to afford a sufficient protection in RA[151] and patients using immunosuppressive drugs.[152] Therefore, second HAV vaccination after 6 months and determination of post-vaccination antibody titers is recommended. If this is not possible, as in the case of a last-minute traveller, one should be aware that an AIIRD patient may not be protected after a single dose of HAV vaccine, and consider passive immunisation prior to the specific journey.

Studies from the different geographical regions across the world reported a variable serological prevalence of HBV infection among AIIRD patients. Data on the efficacy of hepatitis B vaccination in AIIRD patients are lacking, but antibody concentrations are considered to correlate well with protection. Hepatitis B vaccination was immunogenic in most patients with AIIRD,[153–156] although two open label small studies reported an insufficient humoral response to HBV vaccine in AIIRD patients treated with bDMARDs.[157 158] Furthermore, high-dose HBV vaccination did not increase the humoral response rate.[158]

In concordance with the previous recommendations, HBV vaccine should be administered only to patients at risk. Patients at risk include HBV-seronegative patients that travel to or are residents in endemic countries, and patients at increased risk of exposure to HBV (eg, medical personnel, household contacts or sexual partners of known persons with chronic HBV infection, intravenous drug users, men who have sex with men). In case of an exposure to HBV (for example percutaneous (needle stick, laceration, bite or permucosal) in an unvaccinated patient or a patient with an insufficient response to HBV vaccine, a booster or passive immunisation with hepatitis B immune globulin is indicated according to the CDC recommendations.[159]

Herpes zoster vaccination may be considered in high-risk patients with AIIRD

This recommendation remained identical to the recommendation #8 in the 2011 version. The evidence accumulated over the last decade has further supported this recommendation.

AIIRD patients are at increased risk of HZ compared with the general population, with the highest risk of infection in patients with inflammatory myositis and SLE of all ages.[160] A live-attenuated HZ vaccine reduced the risk of HZ by 51% to 70% among immunocompetent individuals 50 years and older in two randomised blinded trials.[161 162] In elderly AIIRD patients,

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vaccination with HZ vaccine was associated with a reduced incidence of HZ over a median of 2 years follow-up, as reported in a retrospective large database study including patients with immune-mediated diseases (RA, PsA, AS, psoriasis, inflammatory bowel disease (IBD)). This effect was present regardless of medication use, including bDMARDs. HZ vaccination offered protection for about 5 years among patients with autoimmune diseases.[53] Furthermore, the vaccine seemed to be immunogenic and safe in a small sample of SLE[54] and in GC-treated patients.[163] Regarding safety, the vaccine was safe within 42 days of follow-up, including for patients on biologics.[53] Administration of HZ vaccine to active RA patients ≥50 years old treated with MTX, 2 to 3 weeks before starting tofacitinib, was reported to be safe and immunogenic at 14 weeks follow-up.[164] Large prospective trials sufficiently powered for assessing safety of this live-attenuated vaccine are lacking.

Based on the increased infection rates, the efficacy in healthy controls and documented efficacy and safety in one study including 463 541 AIIRD patients, including 633 patients on bDMARDS (predominantly tumour necrosis factor (TNF) blockers)), the live-attenuated HZ vaccine may be considered in AIIRD patients. This vaccine is preferably administered 4 weeks prior to initiation of bDMARDs or tsDMARDs,[164] but not during the treatment with bDMARDs or tsDMARDs. In patients with uncertain varicella exposure, evaluation of varicella zoster serostatus may be considered before the administration of live-attenuated HZ vaccine in order to prevent primary varicella infection following the vaccine. There is no enough data on a long-term protection and the need for vaccine booster.

Importantly, a new non-live recombinant subunit adjuvant zoster vaccine called Shingrix was licensed in Europe since March 2018 and available in some countries. The vaccine is recommended for adults 50 years and older, including immunosuppressed patients, and administrated in two intramuscular doses provided 2 to 6 months apart. Shingrix has been shown to be safe and more efficacious compared with live-attenuated vaccine in elderly adults.[165 166] Safety and efficacy of the subunit zoster vaccine have not yet been investigated in AIIRD patients. Based on the fact that Shingrix is a non-live vaccine, it may replace the live-attenuated vaccine in patients with AIIRD.

Vaccination against yellow fever should be generally avoided in patients with AIIRD

This is a newly formulated recommendation. The rationale for specifically addressing the yellow fever vaccine stems from the fact that travelling to the endemic area for yellow fever in the South America and Africa has become popular in the European countries and the question of yellow fever vaccination in patients with AIIRD is commonly raised. A discussion was held regarding keeping the recommendation #12 from the 2011 version that referred to travelling patients with AIIRD. The majority of the panel agreed that the previous recommendation #12 was of a too general character advising to vaccinate travelling AIIRD patients according to general rules, with the exception of avoidance from live-attenuated vaccines. The addition of new, though limited, experience on administration of the vaccine to patients with AIIRD led to a special recommendation for the yellow fever vaccine.

The yellow fever vaccine is a live-attenuated vaccine. A single dose of which is sufficient to confer sustained immunity against yellow fever disease. Primary vaccines typically develop a low-level viraemia, which abates as anti-yellow virus immunoglobulin M (IgM) antibodies develop 4 to 7 days post-vaccination and can persist for several years following vaccination. The vaccine is recommended for people who are travelling to or living in areas endemic for yellow fever virus in Africa and South America.[167]

During the task force meeting, a discussion regarding the safety profile of the primary versus booster vaccination was held. Notably, the booster vaccine was administered without sequelae to 17 Brazilian patients with RA treated with infliximab[168] and 31 Brazilian patients with AIIRD (RA, SLE, SSc, AS), some of them treated with bDMARDs[169] with an adequate immunogenicity in both studies. Yet, these results cannot be extrapolated to immunocompromised individuals receiving yellow fever vaccine for the first time. Notably, 34 French travellers with autoimmune diseases treated with GCs (prednisone or equivalent dosage 7 mg/day) were vaccinated with yellow fever vaccine with an adequate immunogenicity 6 months after immunisation, with a notion of more frequent moderate-to-severe local responses to vaccination, without serious adverse events.[170]

The force task also discussed the option to test for yellow fever immunity by measuring the serology (IgM and IgG specific to yellow fever) prior to the planned vaccination.[171]

In conclusion, patients with AIIRD under immunosuppression should avoid yellow fever vaccination due to the risk of inducing yellow fever infection. For patients with AIIRD travelling to the endemic countries, withholding immunosuppressive therapy to allow a safe vaccination or measuring serology in previously exposed patients may be considered. The duration of withholding of immunosuppressives should be based on the pharmacokinetics of each agent.

Patients with AIIRD, in particular patients with SLE, should receive vaccinations against HPV in accordance with recommendations for the general population

The recommendation concerning HPV vaccination (#9 in the 2011 version) has been modified: instead of considering the HPV vaccine for 'selected' patients with AIIRD, the wording was changed to 'patients with AIIRD, in particular patients with SLE' and the reference to the general population guidance was added. The main reason for this modification was based on the fact that the main bulk of evidence on the epidemiology of HPV in patients with AIIRD is based on studies in female patients with SLE.[172–176] This population is at a particular high risk to contract genital HPV infection, including high-risk serotypes for cervical dysplasia.[173 174] Whereas there is still no data on the efficacy of HPV vaccination in patients with AIIRD, new data on the vaccine immunogenicity in patients with SLE was published since 2010. Overall, the immunogenicity of the HPV vaccine was similar in patients with SLE and controls, without significant safety signals in patients with SLE.[30 177–179] Notably, concerns regarding the safety of HPV vaccine have been raised based by case reports and case series on the onset of autoimmune diseases following HPV vaccination.[180–185] Population based studies have consistently shown that quadrivalent HPV vaccine was not associated with increased incidence of new-onset autoimmune disease in girls and women with pre-existing autoimmune disease.[186–188] Therefore, based on the present data, the task force agreed that HPV vaccination should be encouraged for patients with AIIRD, with a particular focus on patients with SLE, as indicated for the general population.

Immunocompetent household members of patients with AIIRD should be encouraged to receive vaccines according to national guidelines with the exception of the oral polio vaccine

This recommendation, mainly based on expert opinion, is new and follows guidelines of international societies, such as the

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Infectious Diseases Society of America.[189] Immunocompetent individuals, who live in a household with immunosuppressed patients, should receive inactivated vaccines as well as live-attenuated vaccines such as MMR, rotavirus, varicella and zoster vaccine, according to national guidelines. Oral polio vaccine should be avoided due to a risk of transmission to household members, with a small risk of vaccine-associated paralytic poliomyelitis in immunosuppressed household members. Highly immunocompromised patients should avoid handling diapers of infants vaccinated against rotavirus for at least 4 weeks following the administration of the vaccine. Contact with persons developing skin lesions after varicella or zoster vaccines should be avoided.[189]

Live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers treated with biologics during the second half of pregnancy

Since IgG crosses the placenta during the third trimester,[190] anti-TNF biologics, except certolizumab pegol,[191 192] are detectable in newborns of mothers treated with biologics until 6 months after birth.[193] Based on this data, live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers exposed to anti-TNF biologics during the second half of pregnancy.[194–199] Despite favourable data regarding the lack of certolizumab transfer to cord blood, it is limited to a small number of patients[191] and there is no published data concerning live vaccination of the newborns of mothers treated with certolizumab during pregnancy.

A fatal case of disseminated tuberculosis in a newborn exposed to infliximab and vaccinated with BacillusCalmette–Guérin (BCG) vaccine, underlines the importance to avoid live-attenuated vaccines for at least first 6 months of life.[200 201] According to the EULAR points to consider for use of anti-rheumatic drugs before pregnancy, and during pregnancy and lactation, children exposed to biologics only before week 22, can receive vaccinations according to standard protocols including live vaccines. Children exposed to biologics at the late second and during the third trimester, can follow vaccination programme, but should not receive live vaccines in the first 6 months of life.[202] When available, measurement of child serum levels of the biologic in question could guide the decision for or against a live vaccine.[202]

DISCUSSION

The 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD was developed by 21 experts including patients, rheumatologists, immunologists, an infectious disease specialist and HPR representing eight countries. The original set of 13 recommendations published in 2011 was expanded and divided into six overarching principles, followed by nine recommendations. The EULAR task force defined the overarching principles as universal ones to guide vaccination in the AIIRD population, with the first two principles focusing on the responsibility for assessment, education and implementation of the individualised vaccination programme by a treating rheumatology team, jointly shared with and consented by patients. In light of the low uptake of vaccination among the AIIRD population worldwide, emphasising the role of the treating rheumatology team in education of patients and other healthcare professionals regarding vaccines benefits should improve the uptake of vaccination. The following overarching principles were based on the new data related to efficacy, immunogenicity and safety of vaccination under immunosuppressive therapies, specifically addressing the optimal timing of vaccination, the type of vaccine (non-live vs live-attenuated) and the underlying disease activity at the time of vaccination. In line with the 2011 recommendations, vaccination should be ideally administered during quiescent disease, prior to the planned immunosuppressive therapy. Non-live vaccines seem to be safe and sufficiently immunogenic when provided under most immunosuppressive therapies, except for B cell depletion, and probably CTLA4-Ig therapy.

Different from the previous version, current recommendations advocate a more flexible approach to administration of certain live-attenuated vaccines, that is, MMR and HZ. New, but limited, data from the paediatric patients with AIIRD concerning MMR and adult AIIRD patients concerning HZ show efficacy and immunogenicity of both vaccines in patients treated under csDMARDs and bDMARDs.

The core set of recommendations was partially modified compared with the 2011 version, whereas for most recommendations the strength of recommendations remained unchanged, with the exception of HZ. Both influenza and pneumococcal vaccinations are now recommended for the *majority* of patients with AIIRD as opposed to *all* patients, emphasising the importance of an individual infection risk assessment in each case. For example, the risk to contract influenza in a young patient with AS treated with a nonsteroidal anti-inflammatory drug (NSAID) only is not equivalent to a patient with active SLE under immunosuppression. For pneumococcal vaccination, a prime-boost strategy (PCV13 followed by PPSV23 vaccination), a new approach adapted by the CDC for immunosuppressed patients, was presented and discussed. The lack of data on the implementation and efficacy of this regimen in patients with AIIRD was discussed. The choice and sequence of pneumococcal vaccination should be in concordance with local guidelines. The recommendations concerning tetanus, HAV and HBV were expanded to include passive immunisation for selected cases. In the case of HZ vaccination, the sufficient amount of a good-quality new clinical data accumulated over the last decade permitted to upgrade the strength of recommendation to B from C-D in the previous version. Furthermore, new items addressing the vaccination of an AIIRD patient's environment, including household members and newborns of mothers treated with biologics during pregnancy, were added and discussed. The recommendations regarding the BCG vaccine, which is no longer recommended in patients with AIIRD, an approach to hyposplenic/asplenic patients and to travellers with AIIRD were omitted from the present version. Instead, a separate item regarding the yellow fever vaccination in patients travelling to endemic areas was added.

The task force discussed current controversies in the field of vaccinations. In the era of personalised medicine, there is a strong need for a tool to estimate the risk of infection on an individual basis. A tool predicting the probability of contracting serious infections within a specified amount of time will indicate the patients who are most likely to benefit from preventive measures, and accordingly tailor the appropriate vaccination programme and antimicrobial prophylaxis. To date, three scoring systems of serious infection risk were developed in the field of RA, based on the Rochester cohort,[203] large administrative US databases[19] and German Biologics Register RABBIT.[204] A patient's age, functional status, disease severity and activity, comorbidities, previous infections and treatments were considered as contributors to the future risk of infections, with each scoring system using a different model of risk assessment. Notably, the Rochester score did not include treatment with bDMARDs or non-biological DMARDs in contrast to the other two scores. Thus, given the differences in the scoring systems, no direct comparison between them can be performed.

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Yet, these scores represent an important step toward personalised medicine in relation to prevention of infectious disease and avoidance of 'unnecessary' vaccination in AIIRD patients with low risk of infection. Further research is needed to optimise individual risk stratification, enabling physicians to personalise vaccination recommendations in the near future.

The following topics were in particular discussed during the task force: HZ vaccination in the young SLE population and safety of the HPV vaccine. Currently, the HZ vaccine is approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) only for individuals aged 50 years or older. Given the significantly elevated risk of HZ infection and related comorbidities, including the risk of disseminated disease, in the paediatric/young SLE population,[160 205–208] clinical studies are required to evaluate the efficacy and safety of the vaccine in this vulnerable population. This topic may be solved in the future with the introduction of a non-live vaccine against HZ.

Concerns have been raised following the publication of several case reports and series on the onset and exacerbation of SLE after HPV vaccination[185 209 210] and an up to 30% rate of flare in vaccinated patients with SLE in an open study.[177] On the other hand, large scale studies have not shown an increase in the incidence of autoimmune diseases among young females vaccinated against HPV and a case control study on HPV vaccination in SLE patients showed a similar rate of flares in both vaccinated and unvaccinated groups (30). These reports have led the task force to the present recommendation.

In conclusion, the evidence concerning safety, immunogenicity and efficacy of vaccination among patients with AIIRD has markedly grown during the last years allowing to adjust and upgrade the recommendations and guide physicians in the use of vaccinations in AIIRD.

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Correction notice This article has been corrected since it published Online First. Author names have been amended, affiliations updated and the equal contribution statement also added.

Contributors All listed authors of the manuscript are the members of the EULAR assigned task force dedicated to the update of recommendations of vaccination in adult patients with AIIRD. All authors contributed to the formulation of the recommendations. In details, the steering committee of the task force that included convenor (OE), co-convenor (ULM), an immunologist (MB), a specialist in infectious disease (SvA) and methodologists (JL and RL) defined the research questions for the systematic literature reviews (SLRs), that were performed by three fellows (VF, CR, MH), under supervision of the experts in rheumatic diseases (MB) and infectious diseases (SvA). The manuscript was drafted by VF and revised by all task members.

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